MUSCULAR ACTIVITY

THE JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE, LECTURES ON THE HERTER FOUNDATION, SIXTEENTH COURSE, 1924

MUSCULAR ACTIVITY

BY

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PUBLISHED FOR
THE JOHNS HOPKINS UNIVERSITY
BY
THE WILLIAMS & WILKINS COMPANY
BALTIMORE
1926

Fairleigh Dickinson
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TEANECK, NEW JERSEY

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Made in United States of America

Published January, 1926

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BALTIMORE, MD., U. S. A.

THE HERTER LECTURES

In November, 1902, Dr. and Mrs. Christian A. Herter, of New York, gave to the Medical School of The Johns Hopkins University the sum of $25,000 "for the formation of a memorial lectureship designed to promote a more intimate knowledge of the researches of foreign investigators in the realm of medical science." According to the terms of the gift, some eminent worker in Physiology or Pathology is to be asked each year to deliver a lecture at the Johns Hopkins University upon a subject with which he has been identified.

The selection of the lecturer is made by a committee representing the departments of pathology, physiological chemistry, and clinical medicine of The Johns Hopkins University, and if "in the judgment of the committee it should ultimately appear desirable to open the proposed lectureship to leaders in medical research in this country there should be no bar in so doing."

PUBLISHER'S ANNOUNCEMENT

The earlier Herter Lectures, 1904 to 1923 inclusive, have appeared in The Bulletin of the Johns Hopkins Hospital.

The publishers plan to issue the lectures in book form. Announcement of titles will be made as each book is issued from the press.

PREFACE

In the preface to his book "The Respiratory Function of the Blood", Mr. Joseph Barcroft quite rightly tells us that long ago, by spending his leisure in sailing boats, he learnt what he knows (which is no little) of the way to venture beyond the visible horizon. Now, the practice of running is just as ancient and respectable as that of sailing, and the reader may perhaps see signs of the source of my inspiration, at any rate in the fourth lecture of this series: indeed, to tell the truth, it may well have been my struggles and failures, on track and field, and the stiffness and exhaustion that sometimes befell, which led me to ask many questions which I have attempted to answer here. In that attempt, to continue the analogy, I was given a very long start, for Sir Walter Fletcher was my tutor and counsellor at Cambridge and Sir Walter Fletcher's chief pride —in spite of all that he has accomplished in physiology and in the organisation of medical research—is that he once ran for two English Universities against two of the United States.

It was no small honour to be invited to give these Herter lectures, to represent the English Universities not against but before those of America. Yet what one remembers after is not so much the honour as the goodwill and understanding, bred by comradeship and friendly rivalry in discovery. May I therefore acknowledge here, not by name for the list would include the whole of the Medical Faculty and many others, the kindness which I received in October, 1924, from my colleagues in Baltimore.

A. V. Hill

University College, London
June, 1925

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THE DYNAMICS OF MUSCULAR ACTIVITY

FIRST HERTER LECTURE

THE DYNAMICS OF MUSCULAR ACTIVITY

In these lectures I shall deal, not with the whole province of muscular activity, which would require rather a text-book than a series of lectures, but with certain newer aspects of the subject, the mechanical, thermal and chemical, and finally the application to man of the results obtained. In this first lecture I will discuss, not the whole problem of the mechanical response of muscle, but certain developments of the last few years, starting with the capacity of the muscle to do external mechanical work.

Much investigation has been devoted in the past to the mechanical response and characteristics of muscles. These were the easiest properties of muscles to investigate, and represent the final and important results of their activity. It might have appeared, however, that the subject is by now to some degree worked out and unlikely to yield further results of value. Actually, however, in combination with thermodynamical observations and considerations much information has been derived recently from a study of the mechanical output and behaviour of striated muscles. Indeed, in the last few years the investigation of the connection between rate of shortening, or work done, and heat-production has pointed to new, hitherto unsuspected, mechanisms in muscle, which are of considerable theoretical interest and practical importance.

Let us start by considering the muscle as an elastic body. When a resting muscle is stretched the greater the force used in stretching it, the greater the amount of extension, as in any elastic body: and the relation between extension and force (*OA*, fig. 1) may be plotted to give what engineers call a stress-strain diagram; from this the work done in stretching, or the work obtainable from shortening, may be calculated. It was only a step further

to regard the excited muscle as a new elastic body, possessing new elastic properties, and to determine experimentally for it also the relation between length and force exerted at that length. The result gives us what we may regard as a stress-strain diagram for the active muscle, and if we are correct in our hypothesis that the muscle is an elastic body, the work which it can do may be calculated from the area enclosed in the diagram. The work is clearly a function of the size of the muscle, that is, of its length and its thickness, and also of the intrinsic physiological capacity of

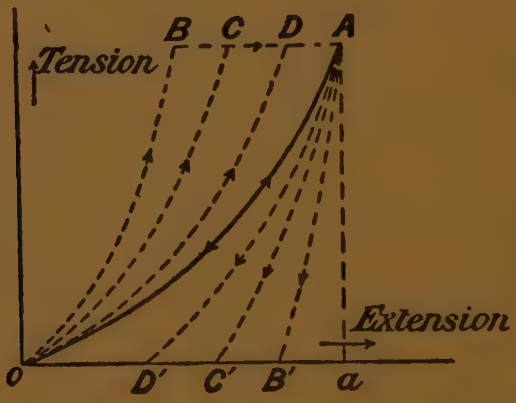

FIG. 1. RELATION BETWEEN TENSION AND EXTENSION IN A RESTING MUSCLE

The full curve *OA* corresponds to a very slow process of unloading or loading the muscle from or to a given tension, and represents a "reversible" process. The broken curves represent "irreversible" processes carried out more or less rapidly. The curves *OBA*, *OCA* and *ODA* correspond to *loading* carried out rapidly, the most rapid being *OBA*, and the least rapid *ODA*. The curves *AB'O*, *AC'O*, *AD'O*, correspond to unloading carried out rapidly, the first being the most and the last being the least rapid. The potential energy possessed by the stretched muscle corresponds to the area *OAa:* the work done in stretching it rapidly along (say) the curve *OCA* corresponds to the area *OCAa;* the work obtained from it on unloading it rapidly corresponds (say) to the area *AC'a:* the work lost and degenerated into heat irreversibly in the complete cycle corresponds therefore to the area *OCAC'*.

(Note: The curves are illustrative only and do not represent an actual observation.) (After Hartree and Hill, 1920.)

its fibres for exerting a force. The simplest way of regarding the matter is to say that the work should be proportional to the product of the length l of the muscle and the force T which it can exert in an isometric contraction. It is then found that the area of the stress-strain diagram of the active muscle is equal to Tl multiplied by a factor

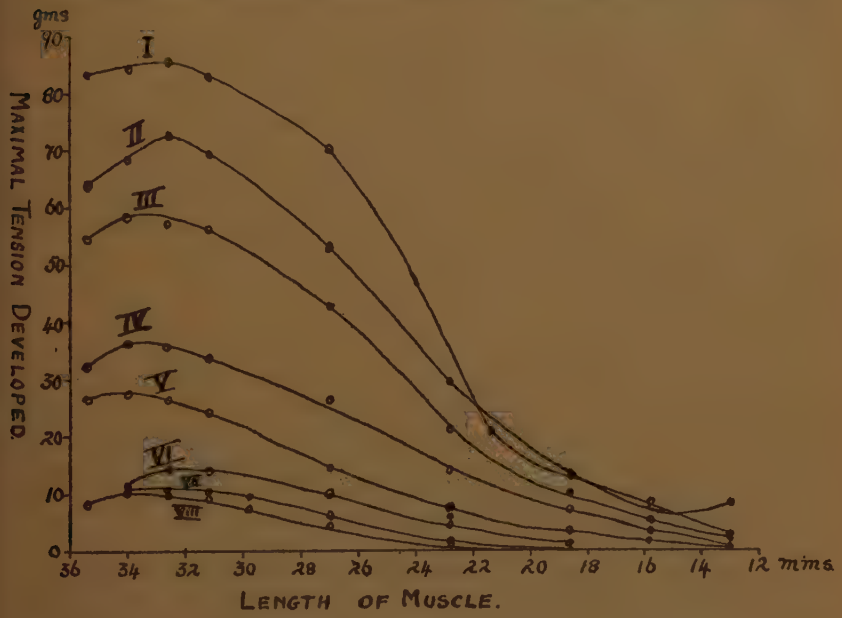

FIG. 2. RELATIONS BETWEEN MAXIMAL TENSION AND LENGTH IN THE PROLONGED CONTRACTION OF A FROG'S SARTORIUS

Curves I to VIII, all of the same shape, were made at various times (0 to 29 hours) after removal of the muscle from the body. (After Mashimo, 1924.)

which is usually (in a twitch) about one-sixth. It is greater in a prolonged contraction. The theoretical maximum work of the muscle excited to a twitch—its potential energy—should thus be expressible as $Tl/6$, and if we wish to compare the mechanical with the thermal response, we should try to relate $Tl/6$ to the heat production. Some years ago I made experiments with the frog's

sartorius on these lines, and, expressing both potential energy and heat in mechanical units, was astonished to find them to be fairly closely equal. On the elastic hypothesis, therefore, the whole of the initial energy of the muscle was liberated as mechanical potential energy, and might conceivably, under the best reversible conditions, be turned into external work. This fact was the starting point of the investigations which we will now discuss.

In actual practice it appeared that the isolated frog's muscle, carrying out an ordinary fairly rapid contraction, was unable to do anything like its theoretical maximum

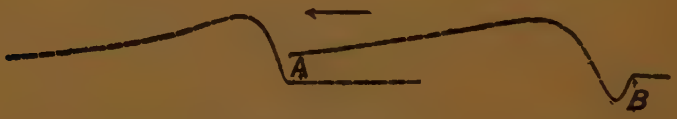

FIG. 3. PAIR OF SARTORIUS MUSCLES FROM RANA TEMPORARIA

Permanent load 5 grams. Galvanometer deflections representing rise of temperature. At the beginning of the left hand curve 155 grams was hung gently on the muscle: the temperature rose. At the beginning of the right hand curve, after the 155 grams had been hanging on the muscle for some time, it was gently removed: the temperature fell rapidly (the reversible thermodynamic effect) and then rose (the irreversible loss of potential energy under viscous forces). Time in secs. shown on the curves. (After Hartree and Hill, 1920.)

of mechanical work: either the elastic theory was grossly at fault and the excited muscle could not be regarded as a new elastic body, or some factor was disturbing the ready transformation of elastic energy into work. To accept the first alternative would have been a confession of failure, since it would have left us without any working hypothesis at all as to the nature of the muscular response. One looked naturally therefore for factors which might account for the large amount of energy used in an actual shortening.

In 1919 Hartree and I came upon certain interesting thermal properties of resting muscles which appeared during passive shortening or lengthening. If an elastic body be

stretched or released it has long been known that certain reversible thermodynamic alterations of temperature result, which were first described by Kelvin. These we found also in our resting muscle. In addition, however, large *irreversible* productions of heat occur when a muscle is stretched or released. These could be associated only with the frictional transformation of mechanical energy into heat in a viscous system, and they led us to the hypothesis that the loss of energy which we required was due largely to such frictional causes. (See also fig. 1.)

It was possible, moreover, that the conditions of loading the muscle, as originally applied, were not satisfactory, that in shortening the muscle was not given at each length the maximum load which it could overcome. The obvious means of supplying the muscle with a load better adapted to its requirements was to oppose it, not by a constant force but by the inertia of a mass. According to Newton's laws of motion, "to every action there is an equal and opposite reaction," so that if a muscle were pulling directly on a freely suspended mass the reaction of the mass would always be exactly equal to the force which the muscle could exert on it. An inertia is the optimum type of load. We constructed therefore, as we found afterwards Fick had done before us, an inertia lever, a freely suspended beam bearing balanced masses against which the muscle could pull, and we recorded the amount of work which the muscle did by seeing how far it could raise a rider hanging on the lever. We obtained in this way larger amounts of work than by other mechanical arrangements for loading, but still nowhere near the theoretical maximum unless the inertia of the lever were made very large and the speed of shortening very small. The rate at which a muscle is able to shorten depends upon the inertia of the lever. With a very light one it shortens rapidly and produces a high velocity in a small mass: with a heavy one it produces a small velocity in a large mass. Had the excited

muscle been similar in its elastic properties to a steel spring, the product $\frac{1}{2}MV^2$, that is the kinetic energy produced in the lever, would have been the same whether the lever was light or heavy. Actually with the muscle it was much greater with the heavier lever. The loading conditions were theoretically the optimum imaginable, so that one could only look, for a reduction in the work obtained, to something analogous to viscosity, or friction, hindering the rapid shortening of the muscle fibres. The muscle

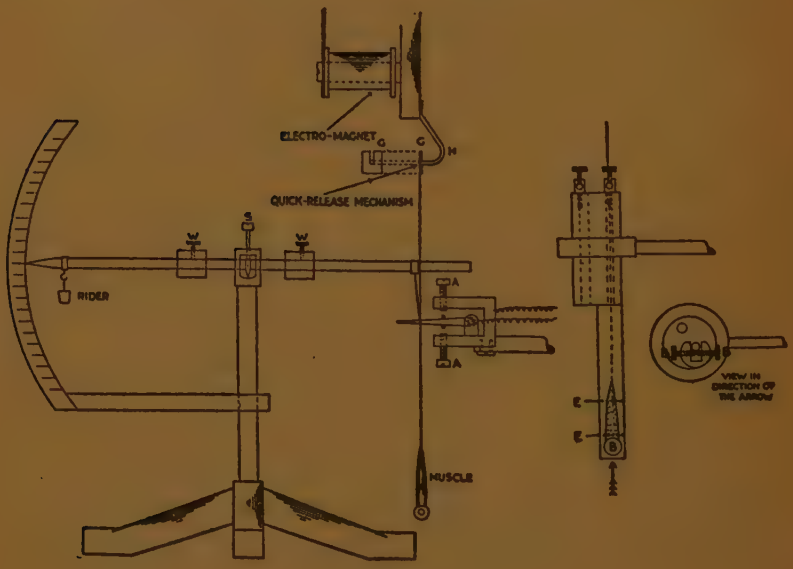

FIG. 4

Left, inertia lever, with weights W, W, and screw S for adjustment of the centre of gravity on to the line of the knife-edges. Rider and scale for measuring work. Lever L with adjustable stops A, A, for (1) limiting the extent of contraction, and (2) electrical timing of the duration of shortening. *Top*, quick-release mechanism, withdrawing the stiff-wire hook H from between the guards G, and so releasing a loop on the fine wire holding the muscle stretched. *Right*, muscle holder for carrying a pair of sartorius muscles immersed in Ringer's solution in a Dewar flask. B, B, vulcanite screws for holding acetabulum; E, E, electrodes passing between the muscles. (After Gasser and Hill, 1924.)

was presumably not simply an elastic system but a "viscous elastic" system, similar to a thin rubber tube filled with thick treacle, in which the more rapid the shortening the greater would be the amount of mechanical energy dissipated in overcoming the inherent frictional resistance of the body itself.

These experiments on the isolated muscle led to an attempt to test the same phenomenon on human muscles. A large and accurately balanced wheel was constructed (fig. 5) against the inertia of which the flexors of the arm could exert a maximal pull. The work done by them was

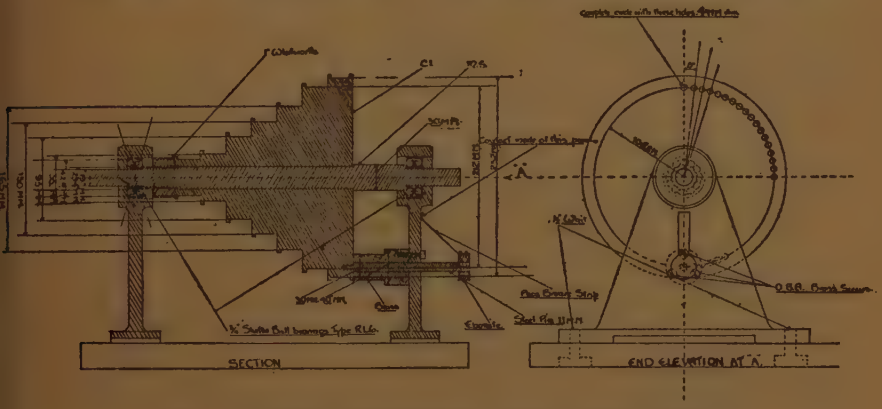

FIG. 5. INERTIA ERGOMETER. (After Lupton, 1922)

measured from the angular velocity produced in the wheel, and the speed of shortening was determined by the breaking of two electric contacts. The speed of shortening could be varied by winding the string which pulled the wheel round one or other of a set of pulleys of different size: on the large pulley the wheel "felt light," on the small pulley it "felt heavy." Expressed more exactly, the "equivalent mass" of the wheel could be varied by varying the diameter of the pulley round which the string was wound. With a large equivalent mass the shortening of the muscles was slow, with a small equivalent mass it

was large, the contraction being maximal in every case. A quick release was arranged by which it was ensured that the maximum tension of the muscle had been attained before shortening was allowed. It was then found that the work done in a maximal effort of the flexor muscles of the arm varies inversely with the speed of shortening, being greater at low speeds, less at higher ones—clearly the same

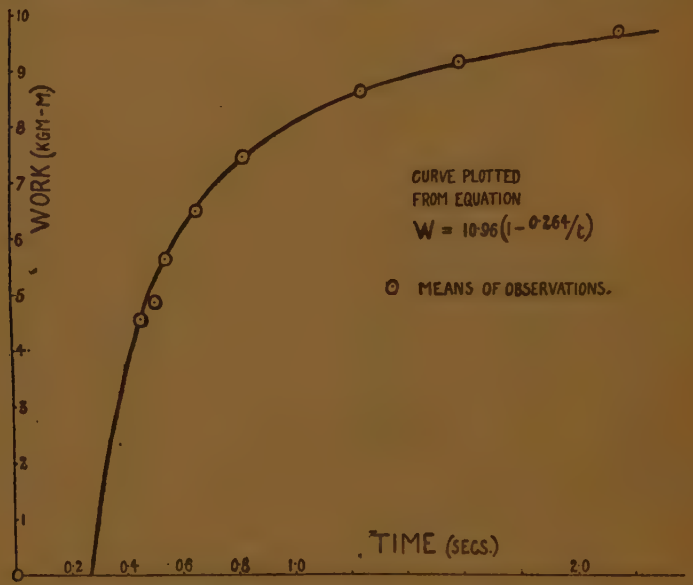

FIG. 6. RELATION BETWEEN WORK DONE AND TIME OCCUPIED IN THE MOVEMENT IN THE CASE OF A MAXIMAL FLEXION OF THE HUMAN ARM
(After Lupton, 1922)

type of relation as we had been led to expect from our experiments on the frog's sartorius. (See fig. 6.) It was natural to conclude that this loss of work at the higher speeds was determined by the viscosity of the muscle substance itself, the work lost being turned irreversibly into heat during the change of form of the shortening muscle.

This change in the amount of work done, with speed of

shortening, has an important application in connection with human muscular efforts of various kinds carried out at varying speeds. Common sense and every-day experience have led people to adopt certain rates at which ordinary movements are performed: the size of a spade is adjusted to give a certain speed of movement when wielded by an ordinary man: the gears of bicycles and of many kinds of machinery are adjusted to attain an optimal speed. The experiments just described afford a scientific explanation of these facts. If a muscular movement be carried out too quickly very little work will be done by it: consequently its efficiency will be low: if it be carried out too slowly a large amount of work will indeed be done, but the amount of energy expended physiologically by the muscle in maintaining its contraction will be too large, and again the efficiency will be low. The maximal efficiency is attained at some intermediate speed, and it is this speed which every-day experience and common sense have led us to adopt in our ordinary working life.

The experiments on man were not conclusive in one direction, since it was possible that the variation of work with speed might be due to some kind of nervous adjustment regulated through the proprioceptive nervous system. A rapid movement of the muscle might stimulate nerve endings in it, or in its tendons and joints, which would cause a reflex withdrawal of innervation from the muscle fibres. The quick release of a muscle, for example, might be very dangerous to an animal, were the whole of the energy of the contracting muscles turned into kinetic energy in the limb; it was possible that a protective reflex would occur, withdrawing the innervation required to maintain the contraction as soon as the latter was no longer needed. The matter could obviously be decided by repeating the experiments on isolated muscles deprived of any possible reflex mechanism. This was the starting point of the experiments which have been performed during the last year by Gasser and myself.

An arrangement similar in principle, though different in design, to the inertia wheel was constructed for the sartorius preparation of the frog. (See fig. 4 above.) The necessary range of equivalent masses was provided, by which the speed of shortening of the muscle after a quick release could be adjusted from very rapid to very slow. It was found that the work done decreased continually as the speed of shortening increased (fig. 7), so that the relation between work and speed was one inherent in the muscle

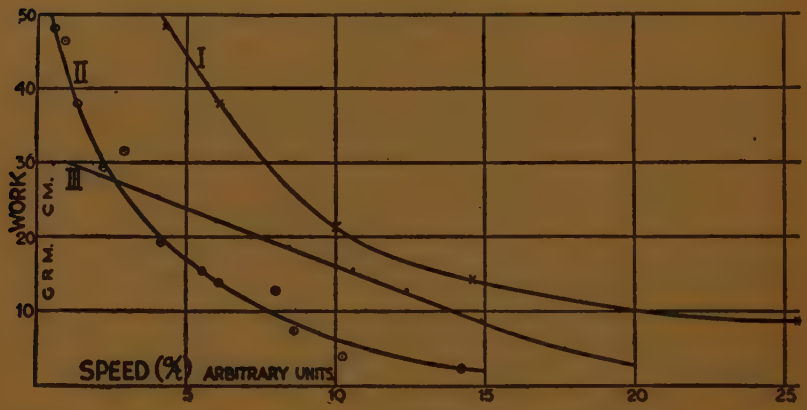

FIG. 7. RELATION BETWEEN WORK DONE ON INERTIA LEVER, AND SPEED OF SHORTENING

Frogs' sartorius muscles stimulated directly and isometrically with maximal tetanus, and released to work on lever only after maximal tension attained. Speed in arbitrary units, a/t, where a = amount and t = time of shortening. (After Gasser and Hill, 1924.)

fibre itself and not connected in any way with the nervous system. If the work varies with speed so also must the force exerted by the muscle during any given element of its shortening: hence the force exerted by the muscle must decrease as the speed of shortening increases. This was the starting point of the next stage.

It is possible in an isolated muscle with parallel fibres to connect one end A to a tension lever, and so to measure the force which it exerts, while subjecting the other end B

to any desired mechanical conditions, such, for example, as allowing it to shorten, or causing it to lengthen, at any desired speed. (See fig. 8.) The muscle is so short and light that the time taken in transmitting to *A* any change in tension produced by the events at *B* is very small. Moreover, the absolute velocity of movement in such a small muscle is so low that no appreciable amount of energy

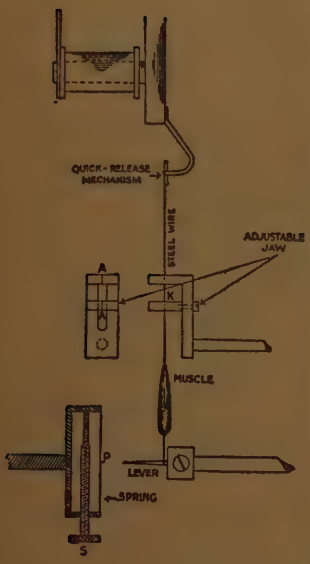

Fig. 8

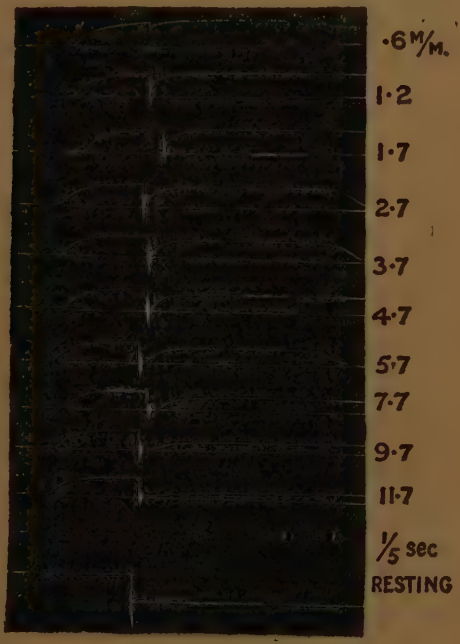

Fig. 9

Fig. 8. Isometric tension recorder. With projection *P* for carrying short bamboo pointer, and screw *S* for keeping spring taut; adjustable jaws for regulating amount of movement of knot *K*; *A*, *A*, slit guides for steel wire connecting muscle to quick release mechanism.

Fig. 9. Effect of quick release on tension recorded in maximal isometric tetanus. Frog's sartorius. Right, amount of release allowed, millimeters. Bottom record, release of resting muscle. Read from left to right. (After Gasser and Hill, 1924.)

appears in the muscle as kinetic energy, even though the duration of its shortening be very small. Hence, even relatively sudden changes at *B* do not cause bad mechanical oscillations at *A*, provided that the tension lever at *A* possesses a high natural frequency of vibration.

The first experiments we made were as follows. A muscle was stimulated with a tetanising current and its tension recorded. It was then allowed suddenly to shorten freely a given small distance; it might have been expected that the tension would merely fall from that corresponding to

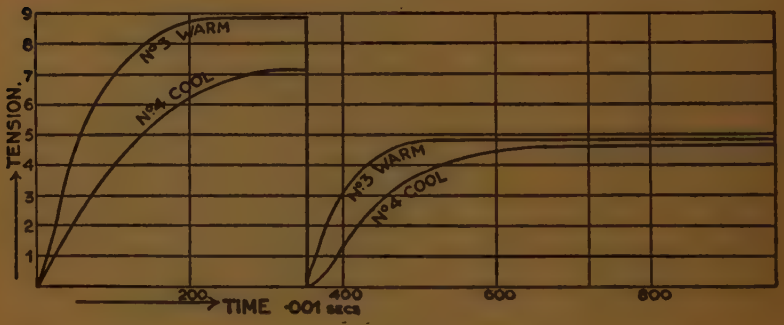

FIG. 10. DIAGRAM COPIED FROM RECORDS OF EFFECT OF QUICK RELEASE

Note that the effect of temperature on the curve of the initial development of tension is the same as on that of the redevelopment after release. (After Gasser and Hill, 1924.)

the greater length to that corresponding to the smaller. It did not. (See fig. 9.) It fell to, or towards, zero and then slowly rose again as the stimulus was continued. The redevelopment of tension was similar under all conditions to the initial development of tension, which occurred when the muscle was first stimulated. (See fig. 10.) If a resting muscle was stretched, and then suddenly released from one length to another, the tension at the second length was attained almost instantly, unlike the case of the stimulated muscle. (See bottom record, fig. 9.) Was the sudden disappearance of the tension in the stimulated muscle,

when released, due to some kind of inhibition of the contractile process by the release, so to speak to letting the steam out of a boiler, so that the pressure had to be redeveloped before the engine could be set working again? The matter was simply tested. If the contractile process

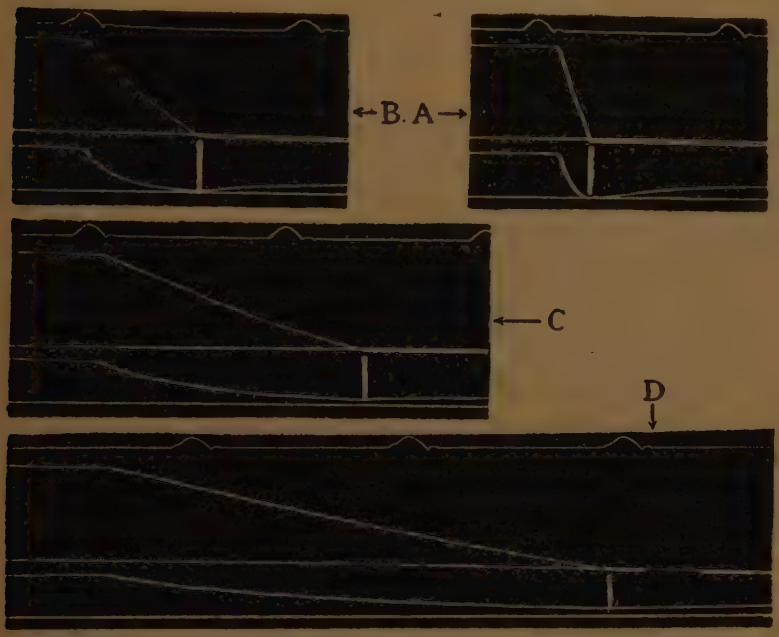

FIG. 11. EFFECT ON FORCE EXERTED BY AN EXCITED MUSCLE OF ALLOWING IT TO SHORTEN AT VARIOUS SPEEDS

Top curve = time ($\frac{1}{5}$ second); middle curve and base line = record of shortening; bottom curve and base line = record of tension. *A* = most rapid shortening, *D* = slowest, *B* and *C* = intermediate. Note that in *A* and *B* the tension falls to zero and then redevelops after the end of contraction, while in *D* the tension practically does not fall at all below its equilibrium value. (After Gasser and Hill, 1924.)

had really been dissipated by the sudden release, then it would not return when the muscle was immediately stretched again. As a matter of fact it returned precisely to its original value, showing that *the active state was still*

present but not manifest externally; the released muscle was still "contracting" though it could exert no external force.

If a stimulated muscle be released not instantly but slowly, the force which it exerts during its release may be recorded by the tension lever at its other end. (See fig. 11.) If the release be very slow the tension falls, so to speak "reversibly," to that corresponding to its shorter length. If the shortening is more rapid the tension falls below its final value and then rises again: the more rapid the shortening, the greater the fall of tension below its final equilibrium value.

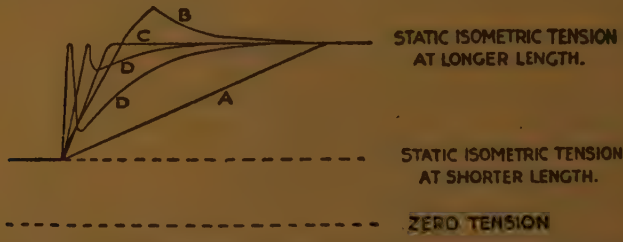

FIG. 12. DIAGRAM OF EFFECT OF STRETCHING AT VARIOUS SPEEDS IN A MAXIMAL TETANUS

A, very slow ("reversible"); *D*, rapid and very rapid; *B*, fairly rapid; *C*, intermediate between *B* and *D*. Frog's sartorius. (After Gasser and Hill, 1924.)

The converse experiment may be made. If a muscle be stretched fairly rapidly (*B*, fig. 12) its tension rises, not to the final equilibrium tension, but above it, and then settles down to that final value along a characteristic curve similar to that of redevelopment of tension after a quick release. If it be stretched too rapidly, other phenomena occur which we were unable to explain, but under such conditions the muscle rapidly degenerates and is often dead after two or three observations only. A very sudden stretch of a stimulated muscle appears to shatter its mechanism. Apart, however, from this shattering by too rapid a stretch, the phenomena of stretching are the converse of those of shortening or release.

It was natural to conclude that the phenomena in question were due in some way to the viscosity of the substance of the active muscle. The much slower return to its final tension, of the stimulated muscle as compared with the stretched unstimulated one, was a sign that the viscosity of the stimulated fibre was much greater than that of the unstimulated. The matter was decided by a direct experiment. A spring was arranged to vibrate and to record

FIG. 13. DAMPING OF OSCILLATIONS IN A SPRING CONNECTED TO A MUSCLE (*a*) UNEXCITED, (*b*) EXCITED AND (*c*) UNEXCITED AGAIN

Note that the damping becomes enormously greater when the muscle is excited. (After Gasser and Hill, 1924.)

its oscillations on a drum. A muscle was connected to it and was alternately stretched and released during the vibrations of the spring. Its viscosity damped those vibrations, and an ordinary damped oscillation was recorded on the revolving drum. (See fig. 13.) The muscle was then tetanised and the damping was found to be increased about 16 times, confirming the deduction from the experiments discussed before. Not only is the active muscle much less extensible than the inactive, but it is *very*

much more viscous. The increase is so large, indeed so startling, that it leads one immediately to ask, what can be the mechanism of this change in viscosity? We shall return to that later.

We attempted then to construct a viscous-elastic model which would reproduce the phenomena shown by a stimulated muscle. A thin india-rubber tube, with walls about the thickness of a child's rubber balloon, was filled with

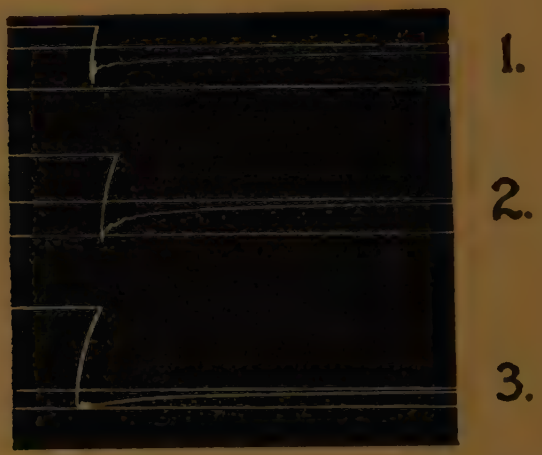

FIG. 14. EFFECT OF QUICK RELEASE ON VISCOUS ELASTIC MODEL

For comparison with figure 9. Upper line, "long" tension; middle line, "short" tension; lower line, zero tension. In (1) and (2) redevelopment of tension commences immediately after release, in (3) only after a certain latent period. (After Gasser and Hill, 1924.)

very viscous material, Chatterton's compound boiled with vaseline, and the same experiments of quick release and slow release, quick stretch and slow stretch, were carried out as we had made on muscle. All the phenomena found in the latter could be reproduced in the model (see, e.g., figs. 14 and 15) and we were led to conclude that the phenomena are indeed of viscous-elastic origin.

If so, we were forced to one very striking conclusion. When a muscle is stimulated its tension develops along a

characteristic curve: when it is released its tension falls to zero and then redevelops along a curve which is identical in shape with that of its original development. (See figs. 9 and 10 above.) If the redevelopment of tension be

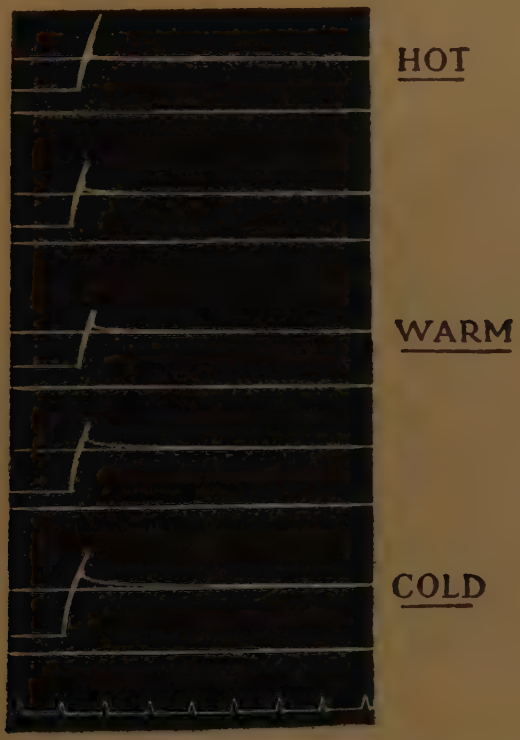

FIG. 15. EFFECT OF QUICK STRETCH ON VISCOUS ELASTIC MODEL

Upper line, "long" tension; middle line, "short" tension; lower line, zero tension. Note rise above "long" tension on stretching, and subsequent gradual disappearance of extra tension. (After Gasser and Hill, 1924.)

determined by purely physical effects in a viscous-elastic medium, we must conclude that the original development of tension is also so determined: the form of the mechanical response in muscle must be mainly conditioned by the elastic state of the stimulated fibres, and by the viscosity

of the substance inside them. The change of state produced by the stimulus must occur much before the mechanical response as ordinarily shown, and the latter must follow the internal change, lagging behind it owing to the viscosity of the medium in which events occur. We were led to look for a sudden change of the mechanical condition of the muscle immediately on stimulation, and re-

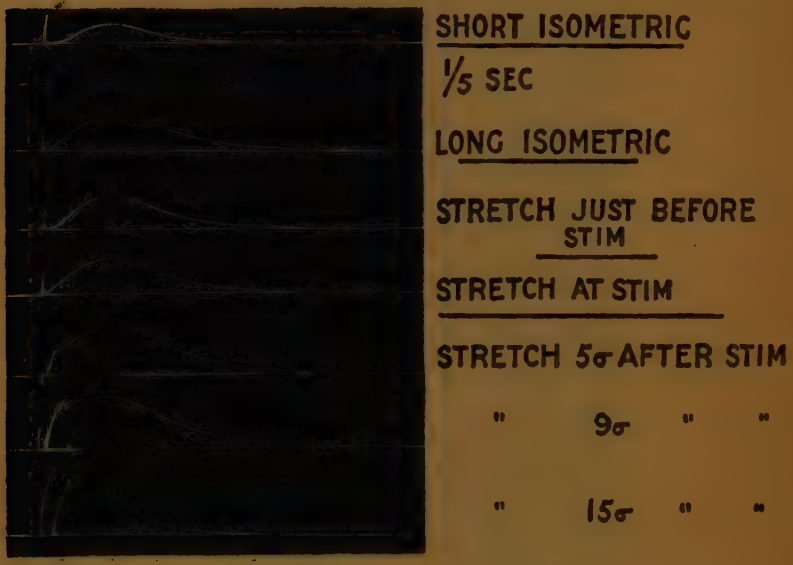

FIG. 16. RECORDS OF THE EFFECT, ON THE TENSION DEVELOPED, OF STRETCHING A FROG'S SARTORIUS MUSCLE AT VARIOUS MOMENTS DURING A TWITCH. (After Gasser and Hill, 1924)

quired a means of studying that without the lag introduced by waiting for the ordinary mechanical response. This means was found in the quick stretch of the muscle.

If a muscle be given a shock its tension rises, and we should expect the effect on its tension of stretching it to be greatest at the moment when it is most inextensible, probably at the moment when its tension is at a maximum. A muscle was stimulated and then stretched at various

moments after the stimulus: also it was stretched and then stimulated. A sudden stretch followed immediately by a stimulus has no effect whatever on the response: the muscle might equally have been stretched minutes before. A stimulus followed immediately by a stretch, however, produces a very large increase in the force developed. If the stretch be delayed, the effect is less. The effect of the stretch is greatest, the increase in tension produced by it is largest, if the stretch come very early after the stimulus. The muscle is most inextensible a few thousandths of a second after it has been stimulated:

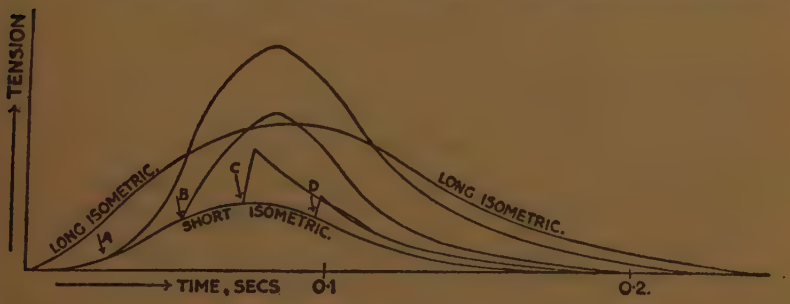

FIG. 17. DIAGRAM OF THE EFFECT, ON THE TENSION DEVELOPED, OF STRETCHING A MUSCLE AT VARIOUS MOMENTS DURING A TWITCH

Copied from actual records. (After Gasser and Hill, 1924.)

it is much more extensible later on. This inextensibility disappears far more rapidly than the mechanical response. We are led therefore by these experiments to the conclusion that the real and fundamental mechanical response, which can be manifested by stretching the muscle out suddenly, occurs much more rapidly and disappears much more rapidly than the ordinary external change which is recorded on an isometric lever.

We have not proposed any final explanation of these phenomena: they obviously require far more investigation. They do, however, suggest that the fundamental nature of the mechanical response is a sudden and reversible gelation

of some constituents of the fibre: due possibly (as Professor Meyerhof has suggested to me privately) to an electrical discharge of charged colloidal surfaces, followed by a dehydration. Imagine that the effect of a shock is to produce instantly, or almost instantly, possibly by the agency of the lactic acid resulting from it, a coagulation of some element of the muscle fibre analogous to the clotting of blood plasma. To consider a definite model, imagine a thin elastic tube filled with blood plasma, and allow the plasma to clot. In the first place, owing to the clot, the viscosity will be greater after than before: in the second place one knows that a clot tends to shrink when formed, its fibrils contract and tend to express the serum. Our model would tend to shorten if its fibrils ran lengthwise in the tube, but the rate at which it could shorten would depend on the viscous resistance of the fluid which had to pass between the ultramicroscopic meshes of its clot. The internal condition might be very suddenly changed, but the external force could not be manifest until the internal stress had had time to overcome the viscous resistance to the necessary change of form. For remember that no contraction is really isometric; the active portions have to shorten, and the inactive ones to lengthen, before the tension can be fully developed externally. If, however, the muscle as a whole were suddenly stretched out, its new rigidity might be made obvious at once, without having to wait for the slow spontaneous shortening of its active parts. We might be able to detect the rapid onset of the clotting by attempting to stretch the clot. We have, if we are to complete the analogy to muscle, to suppose that the clotting is reversible and passes off rapidly as soon as the exciting cause is removed.

We did not propose such a model as an actual theory of contraction: it merely represented the *type* of mechanism which seemed necessary to explain the observed results. It is possible that we are not correct in ascribing all these

curious effects to viscosity. At present, however, we can only say that if it be not viscosity it is something which behaves in a remarkably similar way, a conclusion not unlike the answer to the question of whether it was Homer who wrote the Iliad or whether it was somebody else of the same name. It is obvious in any case that the study of the mechanical properties of muscle is not a sterile subject, and that much remains to be done.

One more remark, this time a piece of almost impertinent speculation. When our viscous-elastic model was stretched if the substance inside it was too viscous the model proceeded

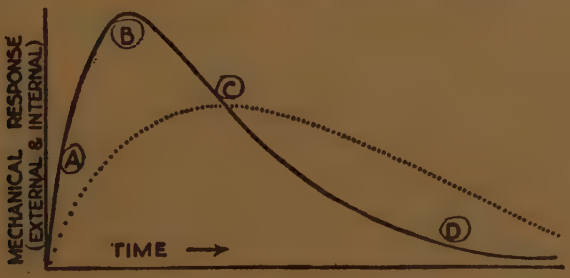

FIG. 18. DIAGRAM OF SUPPOSED INTERNAL ("FUNDAMENTAL") MECHANICAL CHANGE IN MUSCLE

Broken line, observed external response, lagging, owing to viscous-elastic forces, behind the internal change. (After Gasser and Hill, 1924.)

to break up into a series of segments, not unlike what happens in a working intestine. It was impossible, without warming up the model, to make it revert to its previous uniform condition. This tendency clearly could have been counteracted by making the model in "water-tight compartments," providing it with cross-partitions to prevent the viscous material from segmenting. May we dare to suppose that the cross-striations of a muscle, the only clue to whose function is that they are most obvious in the most rapidly moving fibres, are there to divide the fibre into "water-tight compartments," to prevent the irreversible segmentation of its contents?

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THE HEAT PRODUCTION OF MUSCLE

SECOND HERTER LECTURE

THE HEAT PRODUCTION OF MUSCLE

The chief advances during recent years in our knowledge of the intimate nature of muscular activity have come from a study of its thermal and chemical changes. One of the fundamental characteristics of striated muscle and the one involving the greatest difficulty in investigation, is the great rapidity with which events take place in it. There is no doubt that ultimately the muscle is a chemical mechanism, in the same way for example as a Daniell's cell or an accumulator is a chemical mechanism. If we were aware of all the chemical events, we should know all that was necessary about the machine which we are studying. Unfortunately, the investigation of chemical events is a slow and laborious process. Undoubtedly lactic acid, as Fletcher and Hopkins showed some fifteen years ago, is an essential part of the machinery, but it is quite impossible to measure the production and removal of lactic acid instantly and contemporaneously, during and after a single unit of muscular response. It is necessary to evoke a long series of responses and finally to study the gross changes of accumulation or removal of the acid. Attempts have been made to follow the chemical processes involved in muscular activity by studying the changes of hydrogen ion concentration by physical instruments. This would appear to be more hopeful than the possibility of quickening up the study of the reactions by ordinary chemical means, but unfortunately—so far—it has been completely unsuccessful. The instantaneous and contemporary study of the events occurring inside the muscle fibre appears to be possible only in two ways, the mechanical and thermal. The mechanical changes, however, are only the end-products of activity, and if we wish to get inside the mechanism, it is necessary to study some intermediate

process, something occurring between the stimulus and the response itself, something associated with the chemical events which evoke contraction. This is provided by the investigation of the heat-production. It is obvious of course that the picture provided by thermodynamics is only a partial one; the certainty, however, with which the principle of the conservation of energy may be applied, gives us firm ground on which to start our investigations, and there would seem to be no doubt that the outline provided by thermodynamics, once established, must remain, and must finally have the complete chemical picture painted into it. The advantage of the study of the thermodynamics of muscle is that heat may be measured in absolute units, rapidly and at once, and the time course of its evolution analysed by suitable means.

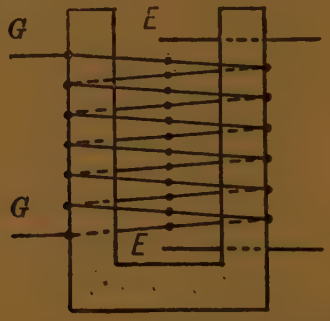
In the study of the thermal changes the most consistent and valuable results have been obtained by utilising the isometric contraction of the sartorius muscle of the frog. That muscle is a very suitable medium for this investigation, in so far as it is practically of uniform cross-section and consists of straight fibres running along its length. The isometric contraction has the advantages, first, that energy is not liberated in it in any other form than heat, so that no complications arise by having to sum the thermal changes with the mechanical work, and second, that in it movements of the muscle over the instruments are prohibited, which (on the small scale of temperature with which we are dealing) is of value in avoiding errors due to temperature differences along the muscle.

The fundamental difficulties in myothermic observation are the smallness of the changes involved and their rapidity. In the muscle twitch of a frog's sartorius at 20°C. the rise of temperature is not more than 0.003°C., and the time occupied in the earlier phases (as distinguished from the recovery process) is only a few hundredths of a second. The first requisite therefore is a very sensitive thermomet-

ric apparatus and great freedom from temperature changes, the second is extreme rapidity and lightness in the recording instruments. Neglecting for obvious reasons the use of ordinary mercury thermometers, there are two possible methods available, those of the resistance thermometer and the thermopile respectively. The resistance thermometer has not been employed successfully in myothermic observations. Calculation with the requisite physical constants shows the existence of a certain fundamental difficulty, which is confirmed by actual experiment. Were it possible to use the resistance thermometer, it would be exceedingly advantageous, as such an instrument may be made very small and light, so that it will respond with great quickness to the temperature changes in its neighbourhood. Moreover, unlimited sensitivity may be obtained by increasing the current in the resistance wire. The fundamental difficulty is that heat is thereby produced in that wire, which is conducted into the muscle and warms it up, causing serious disturbances of the zero, and enormous negative deflections whenever the smallest movement of the muscle occurs. I have attempted recently to use a resistance thermometer for myothermic observations and found it completely impossible. There remains, therefore, only one method, that of the thermopile, which we will now discuss.

It is possible to make a small light thermopile (fig. 1), suitable for myothermic observations, containing one hundred couples of constantan-iron, each providing 52 microvolts for a difference of temperature of 1°C. With a suitable sensitive galvanometer this may give us a scale of temperature in which 1°C. is about 1 kilometre in length. Ample sensitivity, therefore, is available. Such thermopiles are laborious to make by the ordinary method of soldering the wires together, though much of the work hitherto recorded has been done with instruments thus constructed. Recently, however, an ingenious device has

been published by Hamilton Wilson, by which a continuous piece of constantan wire is coated with silver in successive sections by electroplating, and each pair of junctions between a silver-plated and an unplated portion acts as a silver-constantan couple. By this device very small, light thermopiles may be constructed with great ease (fig. 2), and recently several of my colleagues have used such thermopiles in their work. The possibilities now available of myothermic investigation are mainly due to improvements in galvanometers and thermopiles.



Courtesy of the "Journal of Scientific Instruments"

FIG. 1. SOLDERED THERMOPILE

"Warm" junctions down the middle, "cold" junctions on the two sides. *EE*, platinum stimulating electrodes; *GG*, galvanometer leads. (After Hartree, 1924.)

It is not practicable to register the changes of temperature in a muscle as they occur, without lag or loss: the recording instruments are too slow, they possess too great a heat capacity, the flow of heat is not rapid enough and the galvanometer—which must be very sensitive—has too long a period. It is necessary to carry out an analysis of the results obtained, preferably after photographic recording of the galvanometer deflection (fig. 3). The possibility of analysing the time-course of the evolution of heat in a muscle contraction depends upon certain fortunate physical properties of the system employed. The

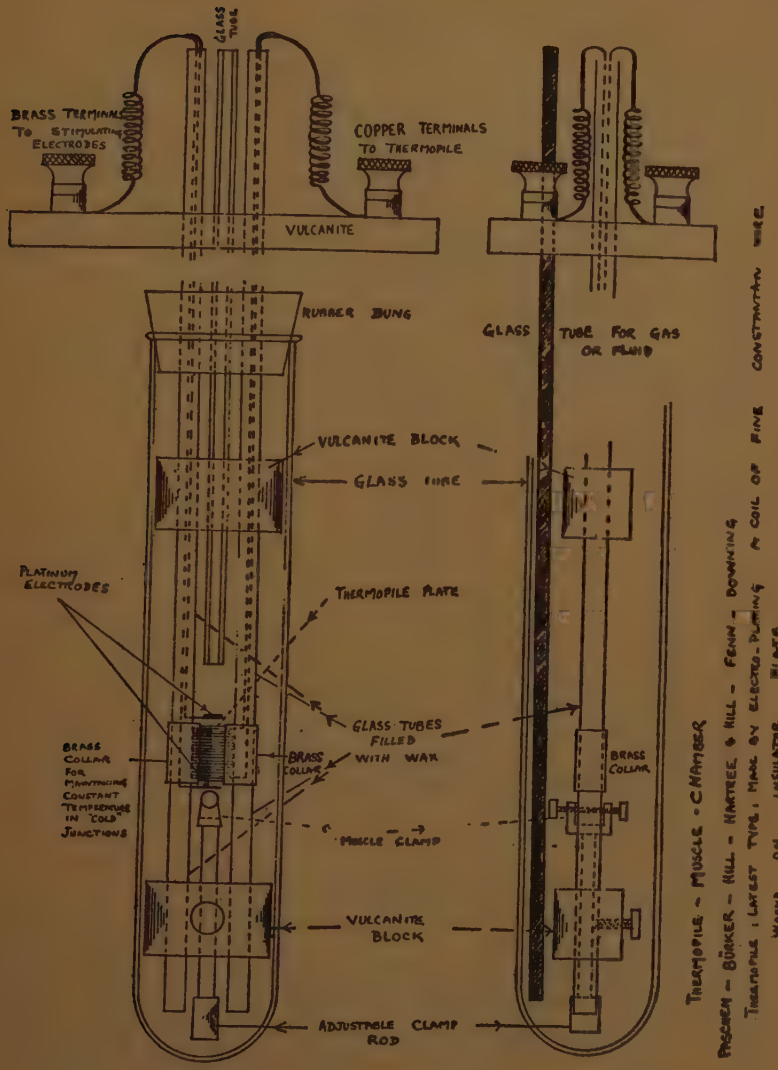

GLASS TUBE
BRASS TERMINALS TO STIMULATING ELECTRODES
COPPER TERMINALS TO THERMOPILE
VULCANITE
RUBBER BUNG
GLASS TUBE FOR GAS OR FLUID
VULCANITE BLOCK
GLASS TUBE
PLATINUM ELECTRODES
THERMOPILE PLATE
GLASS TUBES FILLED WITH WAX
BRASS COLLAR FOR MAINTAINING CONSTANT TEMPERATURE IN "COLD" JUNCTIONS
BRASS COLLAR
MUSCLE CLAMP
VULCANITE BLOCK
ADJUSTABLE CLAMP ROD
BRASS COLLAR
THERMOPILE - MUSCLE - CHAMBER
PIPER - BÜRKER - HILL - NEWTREE & HILL - FENN - DOWNING
THERMOPILE : LATEST TYPE ; MADE BY ELECTRO-PLATING A COIL OF FINE CONSTANTAN WIRE
WOOD OR INSULATING PLATE

FIG. 2. LATEST TYPE OF THERMOPILE AND MUSCLE CHAMBER
Modified from Fenn

conduction of heat, the relation between E.M.F. and temperature, the movements of the galvanometer, its dynamics, the control on it for small movements, and its

damping, indeed, all the factors concerned with the deflection of the galvanometer resulting from the change of temperature of an object in contact with the thermocouple, are governed by linear differential equations with constant coefficients. It is not necessary to know what these coefficients are: they can be eliminated by a "control" experiment: it is essential only that the system employed should possess this general property. The consequence may be expressed in a very simple form. If there be two peculiar sets of heat recorded separately, then the deflections produced, if summed together, are the same as the single

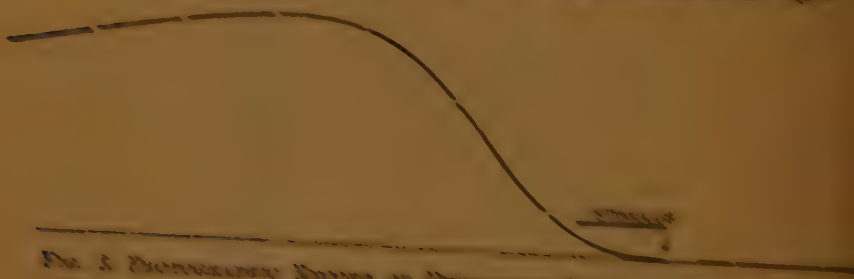
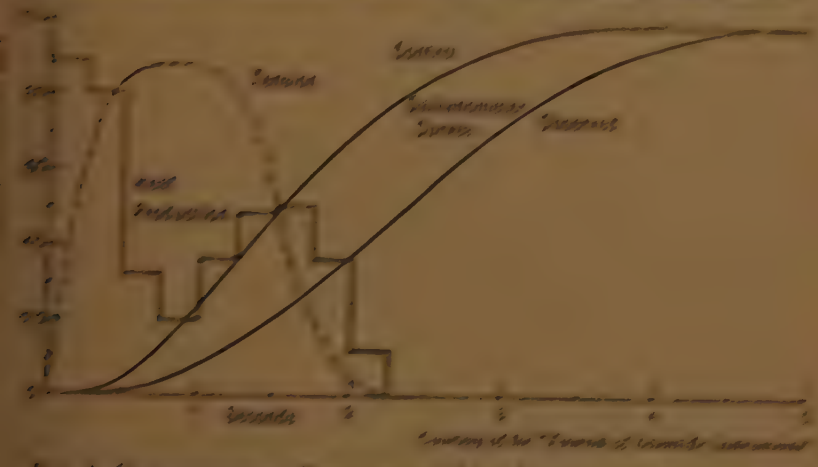


FIG. 5. DIAGRAMMATIC TRACE OF DEFLECTION PRODUCED IN FRESH GASTROCNEMIUS OF FROG BY DEPOSITION OF SUDDEN HEAT AT 30°C. STIMULATION (AS SHOWN) FOR 1 SECOND.

Sensitivity 1 mm. = 1.4×10^{-7} amps. Time marks shown in seconds on the curve. Nickel-coil thermopile with 20 couples. Record about half-size. (After Hartree and Hill, *Jour.*)

deflection which would have been produced if the two heat-productions had been summed together. If the damping had been proportional to the square of the angular velocity of the magnet system, or if the conductance of heat had been proportional to the square of the temperature difference, this fact would not have been true. Expressing the matter mathematically: If $y = f(t)$ be the equation relating the deflection y to the time t for a certain heat-distribution H,* and if $y' = f'(t)$ be the equation for another distribution H', then for a combined distribution

* H also must be regarded as a function of the time.


Seconds

[illegible]

amount of heat. A muscle must first be killed by chloroform, and then an alternating current of known strength must be passed for a known time through the measured resistance of the muscle, so that a definite amount of heat may be liberated, and the resulting deflection of the galvanometer read. A comparison of the two gives the value in absolute units (calories or ergs) of one scale division of the galvanometer. There are various technical difficulties in this calibration which need not be discussed now, but in one modification or another it serves as the basis of all experiments relating heat to work. To some of these I will refer later.

I wish to speak first rather of the analysis of the time-course of the evolution of heat in muscle when stimulated. An amount of heat liberated suddenly at a given time leads to a certain deflection of the galvanometer, $y = f(t)$, which rises to a maximum and falls slowly to zero again owing to conduction away of the heat, etc. A live muscle would give the same shape of deflection, if the heat produced in it were liberated at, or immediately after, the moment of stimulus. In point of fact the "live" deflection differs largely from the "control" one (fig. 4), a fact which can be explained only by supposing that the heat-production in the live muscle is not instantaneous at the beginning, but distributed in time, there being production or absorption of heat later on. It may be said at once that there is no evidence of an *absorption* of heat at any stage in the process, so that nothing but *production* of heat need be taken account of. It is easy enough to produce an apparent absorption of heat, by allowing temperature differences to arise in one's recording apparatus (see fig. 5): such observations, however, are due invariably to an imperfect technique.

One of my earliest observations on the subject was that the galvanometer deflection persists much longer in a live muscle than in a control experiment: it remains away from its zero for periods up to ten minutes, whereas, if the

TO SHOW THE RESULT, EVEN IN AN "ISOMETRIC" CONTRACTION, OF A TEMPERATURE GRADIENT ALONG THE MUSCLE
Stimulus 0·1 sec ; no load. Top of muscle chamber covered
Completely with ice & water ; in vacuum flask at 0°C
Everything carefully as usual, except NO MIXING by
Bubbling
After 3 hours in chamber Zero 400 mm. displaced
And consequent initial negative deflection
On stimulation
Time taps every 0·2 sec ; Stimulus at arrow A
Heat Production
A

Fig. 5

production of heat were instantaneous at the beginning, it would be back to its zero in two or three minutes. This phenomenon can be due only to a delayed production of heat, and I found that this "recovery" heat is appreciable only in oxygen, being abolished by keeping the muscle in nitrogen, or by previous exercise violent enough to use up the oxygen dissolved in the muscle. My original analysis was rough and revealed little but the facts themselves and their order of quantities. It certainly, however, did establish the existence of a "recovery" heat-production, which it was natural to associate—rightly, as it has proved since—with the oxidative removal of lactic acid discovered by Fletcher and Hopkins. A rough estimate of the recovery heat production made it approximately equal to the total initial heat. This estimate appeared to answer unequivocally a question long debated, on the fate of lactic acid in recovery. Fletcher and Hopkins had found that lactic acid is removed in the presence of oxygen, though the same muscle at the end of the recovery process can liberate, during exercise or rigor, the same amount of lactic acid as before. Was lactic acid removed simply by oxidation, or by restoration to the precursor from which it came? Previous experiments had shown that the production of one gramme of lactic acid in rigor leads to the liberation of about 500 calories. Experiments by Peters had proved that the production of 1 gramme of lactic acid in exercise, or in exercise followed by rigor, leads to the liberation of about the same quantity of heat. Hence, if the recovery heat were equal to the initial heat, the oxidative removal of 1 gramme of lactic acid would lead to the production of about 500 calories, which is less than one-seventh of the heat of oxidation of the acid. The conclusion, which, however, was not universally accepted at first, seemed inevitable—that the lactic acid is not removed simply by oxidation. This conclusion has been amply confirmed later by the experiments of Meyerhof.

In a large mass of muscle deprived of its circulation, the rate at which the recovery process can go on, after severe stimulation, depends on the rate at which oxygen can reach the fibres by diffusion. Such are the conditions in calorimetrical experiments. The myothermic method, however, employing small thin muscles subjected only to very short stimulation, makes it possible to follow the recovery process under conditions where its rate is quite uninfluenced

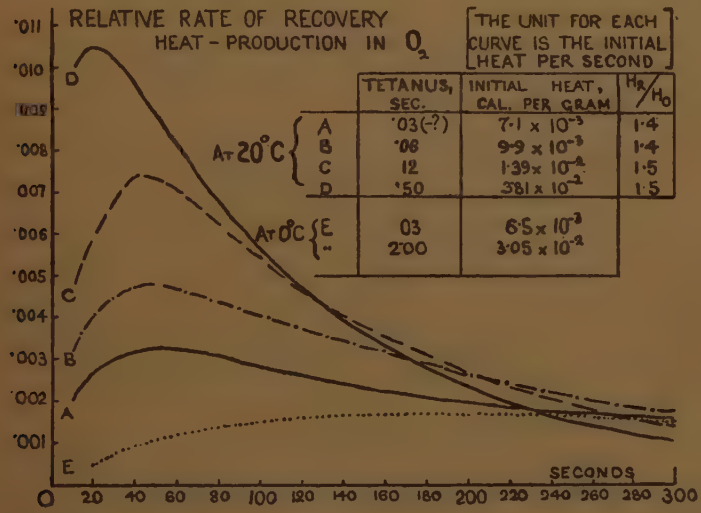


Fig. 6. Recovery Heat-production in Oxygen: Four Durations of Tetanus at 20°C.; Two Durations of Tetanus at 0°C. (Results Coincide.) (Hartree and Hill, 1922)

by any possible lack of oxygen. In such small contractions there is sufficient oxygen already dissolved inside the muscle to account for considerably more heat than the total amount liberated in contraction and recovery. It is possible therefore to follow the chemical dynamics of the recovery process uninterfered with by considerations of oxygen supply. The study of the actual time-course of the recovery heat production has required more elaborate and careful experiments than could be made in 1913, and since

the War I have had the cooperation in this and other matters of my friend W. Hartree, whose skill in experimental work and calculation has made it possible to reach a degree of certainty in the analysis which could never have been attained otherwise. By photographic recording and accurate numerical analysis of the deflection for ten minutes after stimulation, it has been possible to describe the whole

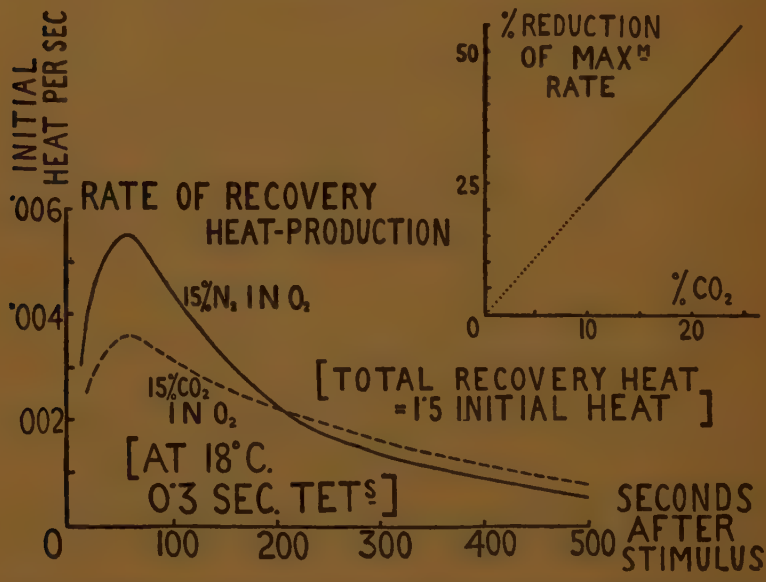


FIG. 7. EFFECT OF CO_2 ON THE TIME-COURSE OF THE RECOVERY HEAT-PRODUCTION

Inset, the effect of varying percentages of CO_2 on the maximum rate of heat-production during recovery. (Hartree and Hill, 1924.)

of the time-course of the delayed heat production. (See fig. 6.) Its absolute magnitude in oxygen is 1.5 times the total initial heat; in nitrogen only 0.25 times; the delayed oxidative heat therefore is almost exactly equal to the total anaerobic heat: its rate is influenced by temperature in the way usual in biochemical reactions, and is decreased by a rise in the hydrogen ion concentration (fig. 7). It

starts from a low rate, rises to a maximum, and declines to zero again. It seems to occur with a velocity approximately proportional to the square of the concentration of the bodies whose removal constitutes recovery. Taking Meyerhof's latest value for the heat liberated per gramme of lactic acid produced, we find that one-fifth only of the lactic acid is oxidised in recovery: the rest must be restored to its precursor.

It is clear that the recovery process is a fundamental part of the whole mechanism of muscle. As we shall see later, oxygen is used only in the recovery process, a fact which has led to a new conception of the nature of the muscular machine.

The analysis of the recovery heat-production is comparatively simple because its evolution is slow. It is desirable, however, also to analyse the production of heat in the earlier phases of contraction, a more difficult matter. After a single shock the muscle shows two phases of contraction, namely, the development and the disappearance of the mechanical response,—contraction and relaxation. Tetanus shows three phases, contraction, relaxation and maintenance. It was desirable to produce an outline of the chemical breakdown processes associated with each of these phases.

A muscle is stimulated, the galvanometer deflects, a curve is recorded on a moving photographic paper. A control curve is made later, after the muscle is dead, for which a known small amount of heat is liberated rapidly, e.g., in 0.1 second, and another deflection is recorded. It is found even in the earliest phases, long before the development of the recovery process, that the two curves differ from one another. The curve for the live muscle rises less steeply and falls less steeply than the control curve, a fact which can be due only to a spreading out of the heat-production. The curves do not differ largely from one another because the whole duration of the initial phase is

so short compared with the time relations of the galvanometer and thermopile themselves: though Hartree is employed at present in improving the latter.[1] The difference, however, is sufficient to make the analysis practicable, and by keeping the muscle at a low temperature it is possible to slow down the events and to attain a greater degree of accuracy in the analysis.[1] That the analysis is really valid has been shown by certain tests recently ap-

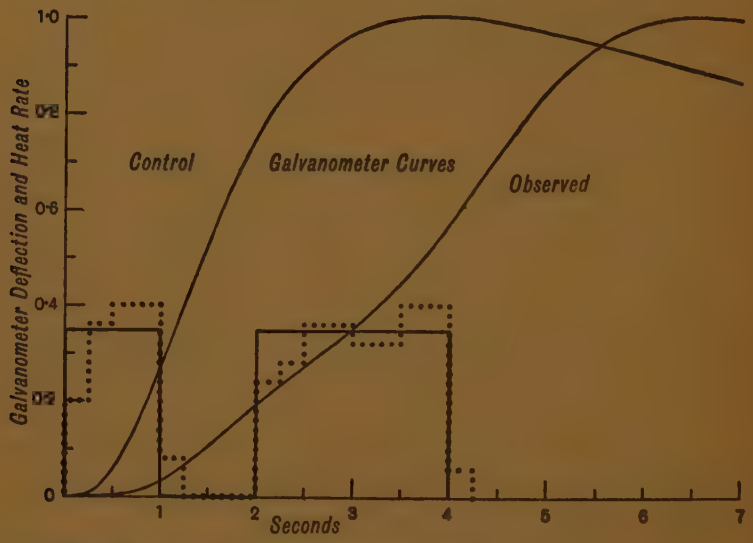


FIG. 8. THE ANALYSIS OF THE DEFLECTION CAUSED BY A KNOWN HEAT-PRODUCTION FOR PURPOSES OF TEST

(After Hartree, 1924)

plied to it by Hartree (fig. 8), in which a known artificial heat production has been analysed with reasonable exactitude from its records. The result that appears is that during the development of the contraction there is a large

[1] Considerable improvement has recently resulted also from (1) increasing the figure of merit of the galvanometer system: A. C. Downing has constructed a galvanometer with a figure of merit of 18,000, which moves about 4 times as rapidly, at the same sensitivity, as the instrument previously employed; and (2) using slower muscle, the *biceps cruris* of the tortoise.

outburst of heat, during the maintenance of the contraction there is a continued production of heat, reaching a constant rate as the contraction is prolonged, and a comparatively large and sudden evolution of heat during relaxation (fig. 9). An excited muscle behaves like an excited electro-magnet: energy is required to magnetise the iron and to make it develop its pull: energy is required to cause it to maintain

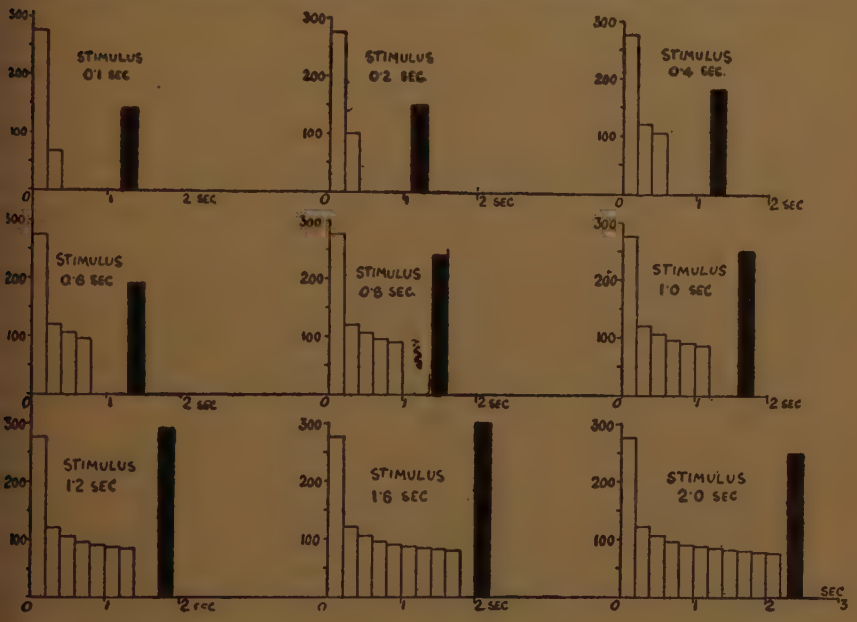


FIG. 9. HEAT LIBERATED BY SARTORIUS MUSCLES AT 0°C. IN OXYGEN

The height of each rectangle represents the heat given out in the interval corresponding to the base on which it stands. Skeleton rectangles represent the heat liberated during contraction, black rectangles the heat liberated during or immediately after relaxation. (After Hartree and Hill, 1920.)

its magnetic condition and to continue its pull; heat is liberated when the magnetic condition, and the energy associated with it, disappear as the current is cut off. In the muscle energy is required to set up the contraction, and, as we shall see later, more energy is required if work be done. Energy is needed to maintain a contraction, as,

indeed, we know in our own bodies when we try to hold a weight for a long time. During relaxation the potential energy of strain possessed by the muscle during contraction has to disappear, and we find it as heat.

Perhaps the most important point brought out by this analysis of the initial heat-production is that relating to the influence, or rather to the absence of influence, of oxygen. The essential conclusion can be drawn without any analysis, merely by comparing the curves of deflection with and without oxygen. The proof that oxygen has no effect whatever on the *time-course* of the initial heat-production complements an observation by Weizsäcker, working at Cambridge in 1914, that the presence or absence of oxygen has equally no effect on the *magnitude* of the initial heat-production. No difference whatever can be detected between the curves obtained (*a*) from a muscle in pure oxygen and (*b*) from one which has been deprived of oxygen in the most rigorous manner for several hours. The conclusion is important and supplements the observations previously described on the recovery heat-production. Oxygen is not used at all in the primary breakdown but simply in the recovery process. A muscle behaves like an accumulator, which can be discharged without any kind of combustion or any kind of provision of energy from without: it requires external energy only when it has to be re-charged. It had long been known, of course, that muscles can go on working for some time in the absence of oxygen, but it was open to anybody to suppose that the processes in the presence and in the absence of oxygen were different. So they are, to the extent that recovery follows one but not the other; the complete absence, however, of any effect of oxygen on the initial processes of contraction shows that those initial processes are identical in both cases. The analogy of the accumulator is exact.

If we take the case of the prolonged isometric contraction, heat is liberated in each of the three initial phases

of contraction, maintenance and relaxation. If the contraction be maintained for a long time, there is a steady heat-production during the whole of that time, propor-

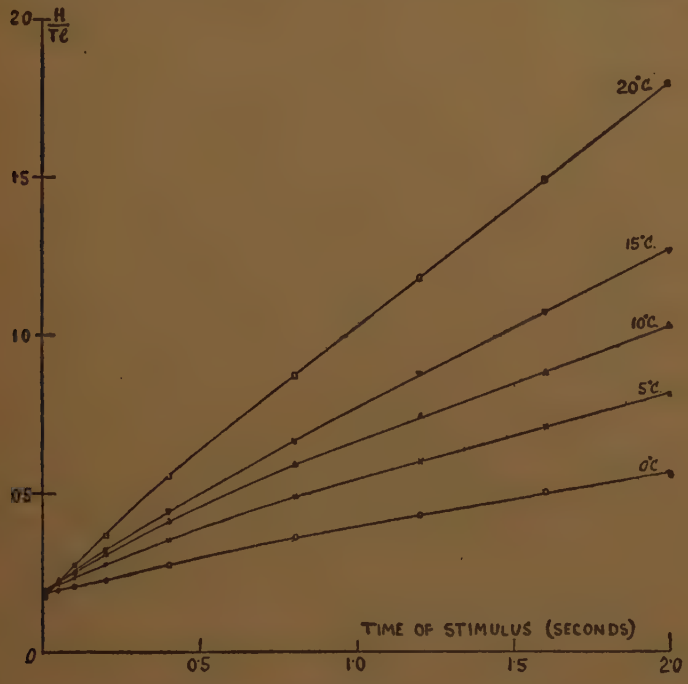


FIG. 10. RELATION BETWEEN H/T1 AND DURATION OF STIMULUS, FOR DIFFERENT TEMPERATURES

The curves all start from the same point, corresponding to H = T1/5.5, and rapidly become linear. (After Hartree and Hill, 1921.)

tional to the tension developed (fig. 10). We may describe the phenomenon mathematically in the formula:

$$\frac{H}{Tl} = A + Bt$$

where H is total heat-production, T is force developed, l is length of muscle, t is time during which the contraction is maintained, and A and B are constants. It is found

that A is independent of temperature, having, in the case of the sartorius muscle, always a value of about 1/5.5; B, which we may regard as the inverse of the "efficiency of maintaining a contraction," depends on the type of muscle, on temperature, on fatigue, and on many other factors.[2] If we apply this result to the important practical case of human movements, so much energy is required to set them up, so much to maintain them for a given time. The amount required to set up a given contraction is constant, the amount required to maintain it is variable, depending on the nature of the muscle and its condition at the time. Anything which slows the single twitch of a muscle makes summation more easy and B smaller: the muscle becomes more efficient for maintaining a contraction. The quickest muscles of all are the least efficient when it comes to exerting a force for a long time.

It has often been discussed whether the mechanical response and the internal metabolic changes which precede it may be separated from one another. If it were possible to have a thermal change, signalising chemical reactions inside the muscle, without any external mechanical effect, it would provide a most valuable method of research and allow us to draw conclusions of considerable importance. For example, if, as has been asserted, a muscle may still produce considerable quantities of heat at a moment when it can exert no tension at all, then it would be of first-class interest to find whether the electrical response may still occur. We could thus decide whether the electric change accompanies the chemical reactions, or only the mechanical response. Unfortunately for the interest of the subject no means of separating the internal metabolic changes and the external mechanical changes has ever been found. Experiments in which the separation was alleged have been

[2] A has approximately the same value, in the *biceps cruris* of the tortoise, as in the sartorius of the frog. B in the frog may be many times as great as in the tortoise.

found to be incorrect. In a most careful series of experiments Gasser and Hartree recently proved that when a muscle is caused to diminish its response reversibly by alcohol or hypotonic solutions, the heat and tension disappear together. Even the highest sensitivity of the methods available only showed that the line relating heat to tension passes through the origin.

The same effect obtains in connection with the action of drugs. If a contracture is produced, one may always safely look for an accompanying heat production. Veratrin has been said to delay relaxation and so to cause its characteristic prolonged contraction. This is definitely untrue. It is possible to analyse the course of the production of heat during veratrin contracture, and it is found that the rate of heat production runs parallel to the tension maintained throughout and that the ratio of the two is not only constant but has identically the same value as obtains during the contracture of a tetanus. The precise details of the working of veratrin remain to be investigated, but in a general way it is certain that it merely liberates continuously the chain of processes normally released discontinuously by a shock or a series of shocks. In the normal muscle a shock causes a momentary opening, which is followed by the rapid closing, of the door through which energy can pour in the form of lactic acid and heat. In the veratrin contraction the door is opened but the closure is only slow. The energy may escape continuously and produce tension continuously, and the relation between the two is the same as in an ordinary tetanus. Caffein shows an analogous effect. Soaking a muscle for a few minutes in 0.05 or 0.06 per cent caffein leads to the slow development of a typical contracture. Matsuoka has supposed that the course of this contracture is determined by the admission of caffein into the muscle. This is definitely not the case. The contracture develops in an hour or two even when the muscle was previously soaked only for

five minutes in a caffein solution and then removed to air. Apparently the caffein gradually changes the permeability of the surface which restrains the free passage of lactic acid, gradually opens the door which normally controls the outflow of energy, so that there is a continual escape, slower indeed but more persistent than that of the veratrin contraction, and leading in the end to the lactic acid maximum, to final rigor. The whole process is accompanied by an evolution of heat and a production of lactic acid; the maximum of contracture occurs at the same moment as the maximum of heat rate. Caffein appears merely to release slowly and continuously the chemical events which normally occur only rapidly and discontinuously on stimulation. The whole curve of heat liberation after caffein may be reproduced by applying a shock every few seconds and so maintaining a continual release of energy.

A prolonged contraction may be produced in still another way, namely, by soaking the muscle, not in normal Ringer's solution, but in one of NaCl. The muscle in pure salt solution shows a more prolonged contraction, often a contracture analogous to that produced by veratrin. Again we find (Sereni) that this prolongation of the mechanical response is accompanied by an increase in the amount of heat liberated and (Hartree) by a prolongation of the heat production. It is difficult not to come to the conclusion that whenever we find prolonged contraction—at any rate in a voluntary muscle—there we shall find also a prolonged evolution of heat and a prolonged liberation of lactic acid.

We have dealt so far, for several reasons, with the simple case of the isometric contraction: first, because it involves us in one less variable, namely, the length of the muscle, and second, because myothermic experiments in the isometric contraction are so much simpler and freer from the possibility of error. Recent developments, however, of the technique have made it possible to study the heat-

production in a muscle which is allowed to shorten as much as one desires, and *provided that stringent precautions be taken*, reliable results are obtained. The temperature equilibrium in the muscle chamber must be so good that shortening over the junctions of the thermopile does not bring cooler or warmer parts of the muscle into contact with them. It must be remembered that this constancy of temperature must be to the nearest 1/100,000 of a degree because our scale of temperature is so small: one must beware of trusting to one's "common sense" in the matter. During the last two years Fenn, followed by Azuma, has studied the effects of shortening and doing work upon the total liberation of energy by a muscle. Fenn found, in a very important series of experiments, that when work is done, there is an "excess" liberation of energy over and above that necessary in an isometric contraction of the same duration (fig. 11). The muscle is excited and allowed to shorten from one length to another length, to lift various loads from one to the other. The work done is proportional to the load. If the load be held up at the end of the contraction so that the muscle relaxes unloaded, the excess energy is just about equal to the work done. If the muscle contracts freely and then lowers the load, excess energy is liberated of the same order of size as the work done by the load in falling: the muscle requires energy both to lower and to raise a weight. This is one only of the curious and important results which Fenn found. If a muscle be caused to *lengthen* during the development of its contraction, it gives out less energy than in an isometric twitch. If it be held fast initially and allowed to shorten during relaxation only, then again it will give out less heat. Shortening during contraction, lengthening during relaxation, appear to require excess liberation of energy. Lengthening during contraction, shortening during relaxation, appear to cause an excess "absorption" of energy, i.e., to lead to a total energy liberation less than that of the isometric twitch.

We are studying here the curious power which a muscle possesses of adapting its liberation of energy to the work it has to do. We are dealing obviously with a very fundamental property of the machine. For those who like mechanical and electrical analogies the case of the electric motor may be suggestive. If the motor be run unloaded,

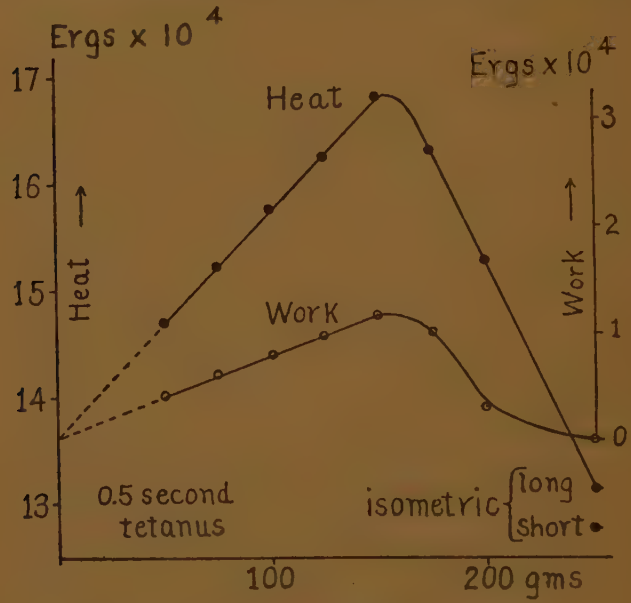


FIG. 11. VARIATION OF HEAT WITH WORK

Shortening limited to 2.66 mm. After-loaded isotonic contraction: work varied by varying load. The work curve falls off at the point where the load becomes too heavy to be lifted the full distance. (Fenn, 1923.)

a certain amount of energy is used: increase the load and the motor automatically takes more current: try to drive the motor from without and a back E.M.F. is produced, causing less current to be taken. It is clear, in any case, that the "all or none" principle is not completely applicable to the muscle fibre, *if we state the principle in the form that the response depends only on the stimulus and on the initial*

circumstances. The amount of energy which the muscle gives out obviously depends on factors which come in *only after the muscle has begun to shorten,* on the inertia opposing its contraction, on the load it has to lift. State it in the form that *the response of a single muscle fibre cannot be varied by varying the stimulus only* and it still holds. It is clear also that the hypothesis that a stimulated muscle is simply a new elastic body is more complex than we thought. A muscle may possess elastic properties, but it requires more energy to do more work, a fact which is very difficult to reconcile with the simple elastic body theory. Perhaps the experiments of Azuma, amplifying those of Fenn, may afford the first clue in a very mysterious problem.

I referred in my first lecture to the curious thermoelastic phenomena which occur when a muscle is released or stretched. Stretch a muscle and its temperature rises: release it and its temperature falls, both events being reversible ones in the thermodynamic sense, both, however, being followed by an irreversible process in which mechanical energy is degraded into heat owing to the viscosity of the muscle substance. These reversible productions or absorptions of heat are not small and may very well play a part in the phenomena described by Fenn. They depend upon the coefficient of thermal expansion of the elastic substance which is stretched. If the elastic body expand on heating, then on stretching it, it will cool. If it shorten on heating, then on stretching it, it will warm, in either case by an amount directly proportional to the coefficient of thermal expansion. Persisting with our view that the muscle is an elastic body, the stimulated muscle has apparently different elastic properties from the unstimulated, and the coefficient of thermal expansion also is presumably different. The coefficient of thermal expansion of resting muscle is opposite in sign to that of most known substances. It may well be the case that in

the transformation from rest to activity the more normal type of coefficient will appear, so that the muscle may cool when stretched and warm when allowed to shorten, and that during relaxation there may be a gradual return from the one type of coefficient to the other. That such an explanation is required is suggested very strongly by the

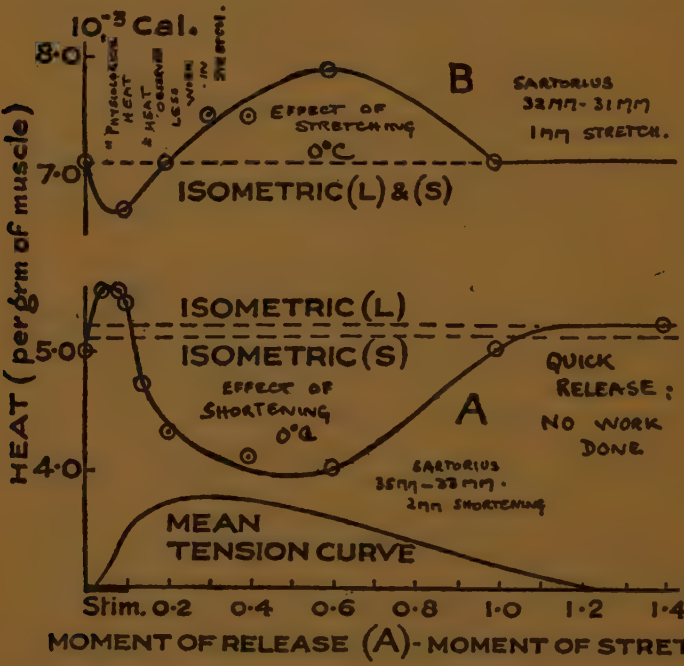


FIG. 12. EFFECT ON THE BEST PRODUCTION OF STRETCHING OR RELEASING A MUSCLE AT VARIOUS MOMENTS DURING AN OTHERWISE ISOMETRIC TWITCH

(After Azuma, 1924)

experiments of Azuma (fig. 12). The thermal effects of the quick release at various moments during a twitch are complex, but they are the exact converse of those of a rapid stretch. It is difficult to see any explanation of Azuma's results except a thermodynamic one. To assert merely that the muscle adapts its energy output to the

work it does would be an expression of ignorance. Such may be a fact, but even so the adaptation must have some mechanism behind it, and thermodynamics and these thermal properties of elastic systems may be expected to provide us with an explanation of the mechanism.

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THE CHEMICAL CHANGES ACCOMPANYING MUSCULAR ACTIVITY

THIRD HERTER LECTURE

THE CHEMICAL CHANGES ACCOMPANYING MUSCULAR ACTIVITY

INTRODUCTION

The closing years of the nineteenth century marked what seemed to be the final establishment of a particular conception of respiration in muscle. It appeared to be established that muscular energy sprang from a more or less explosive splitting of some molecular complex, which had been built up into some highly unstable form, by the inclusion within it of oxygen taken in by the cell during rest. The breakdown of this hypothetical molecule was supposed to yield both lactic acid and carbon dioxide, these being the two obvious and recognisable products of activity.

This conception, in its earlier stages, connected the idea of "irritability" with that of combustibility. Spallanzani, however, showed that living tissues can long survive and continue to yield carbon dioxide without any contemporary supply of oxygen. Various workers found the same to be true of muscle, and it was on this that Hermann chiefly based his theory of inogen. He showed in 1867 that free oxygen is not present in the air pumped from isolated frog's muscle, and yet that without any supply of oxygen from outside carbon dioxide is yielded by the muscle when it contracts or stiffens after death. At the same time lactic acid is produced, while no other recognisable chemical changes occur. Inogen therefore was the unstable precursor both of lactic acid and of carbon dioxide, a precursor in which oxygen was ready to combine explosively with carbon and hydrogen in the combustion which was to yield the energy of contraction. After the explosive breakdown of this precusor, it was supposed that fresh car-

bon bodies, and perhaps also the lactic acid, were combined again in a newly oxygenated unstable molecule of inogen.

This inogen hypothesis of Hermann was taken up again later by Pflüger but without significant change, or fresh experimental support. Pflüger's "giant" molecule, as he described it, made unstable by the inclusion within it of what he called "intra-molecular oxygen," was the same in all essentials as the inogen molecule of Hermann.

These conceptions of Hermann and Pflüger have had a historical importance reaching far beyond the particular enquiry into muscular energy. They summarised the only aspects of cell metabolism which had received any experimental analysis at all, and up to the end of the nineteenth century they not only represented all that was known of cell respiration and of its relations to cell energy, but they dominated also our ideas of cell metabolism in general. Yet, in the course of the last quarter of a century they have been proved completely false.[1]

It is not necessary to go specifically into the accumulated evidence against these theories. The work of Fletcher, of Fletcher and Hopkins, of Meyerhof and of others, has shown that all the carbon dioxide which can be obtained from a muscle in the complete absence of oxygen was there pre-formed in chemical combination: that the lactic acid which appears arises, not from any mysterious complex but from glycogen: that the energy liberated in the anaerobic contraction can be explained completely by the formation of sodium lactate from its known precursors, without leaving a balance for any other reactions, whether oxidative or not: and that the oxygen taken in by the surviving isolated muscle is used completely in the oxidation of carbohydrate, without any remainder for storage in an intra-molecular form. The change of outlook is complete.

[1] This account of the theories of Hermann and Pflüger has been taken from the Croonian Lecture by Fletcher and Hopkins. Proc. Roy. Soc., 89B., p. 444, 1917.

THE EFFECTS OF OXYGEN UPON MUSCLE

The change of outlook started from the experiments of Fletcher, on the gaseous exchanges of the isolated muscle, and on the effects of oxygen in delaying loss of irritability. A muscle left in nitrogen gradually stiffens and contracts: left in oxygen it remains flaccid without shortening: forced by stimulation towards stiffening it may be recalled by oxygen to its previous flaccidity. In oxygen its carbon dioxide output is increased. All this seemed to point to the oxidative removal of some product of activity, which is the basis of stiffening and fatigue.

Now lactic acid itself is the most obvious cause of the slowing of fatigue and of the stiffening of rigor mortis. Its artificial application can mimic the signs of both. Fletcher's results led irresistibly to the conclusion that lactic acid produced by activity is oxidisable, or in some other way removable by oxygen, with an accompanying production of carbon dioxide. The next step was to obtain direct evidence of the changes undergone by lactic acid in the muscle. That step we owe to the classical investigation of Fletcher and Hopkins published in 1907.

LACTIC ACID IN MUSCLE

Up to the time of Fletcher and Hopkins's investigation there was hardly any single statement made with regard to the conditions of lactic acid appearance in muscle which was not both supported and contradicted by rival sets of observers. The inherent difficulty besetting the chemical examination of muscle lay in the fact that the necessary processes of extraction cause, at the moment of their application, profound structural and chemical alteration. The realisation and the overcoming of these difficulties is one outstanding merit of Fletcher and Hopkins's work. Since 1907 the methods of studying lactic acid in muscle have been considerably quickened and improved by others,

especially by Meyerhof, and the investigations of the latter have helped to complete the structure of which the foundations were laid by Fletcher and Hopkins in 1907. It was their pioneer work, however, which gave the initial impulse to all the work on which our present knowledge of the intimate chemical behaviour of muscles is based.

THE CHEMICAL PROCESSES OCCURRING IN THE ABSENCE OF OXYGEN

I will cease now to follow the order of discovery and will describe the facts in their logical and not in their historical sequence. We will consider first the processes which occur in the complete absence of oxygen.

When a muscle is excited and fatigued, or sent into rigor by heat, chloroform or other similar agencies, or allowed to undergo a prolonged process of anaerobic survival, definite changes are recognisable:

(*A*) Glycogen disappears.
(*B*) Lactic acid appears in equivalent amount.
(*C*) Preformed CO_2 is driven off.
(*D*) Heat is produced proportional to the lactic acid formed.
(*E*) The hydrogen ion concentration rises.

The same amount of heat is liberated, per gram of lactic acid produced, whether as the result of stimulation, of survival, or of rigor. Clearly the same chemical process occurs in every case. Some 370 calories accompany each 1 gram of lactic acid, by whatever process the latter is formed, provided that no oxidative reactions are allowed.

These are the only chemical reactions known definitely to occur. According, however, to Embden and his coworkers another process accompanies activity, the breakdown of a somewhat mysterious hexose diphosphate ("lactacidogen") which they believe to be the immediate precursor of lactic acid. They have succeeded in isolating an osazone from muscle similar to that of hexose diphosphate, and have found that all the processes which liberate

lactic acid result in the disappearance of their lactacidogen. Unfortunately the amount of hexose diphosphate present in muscle at any time is not capable of immediate and direct estimation: it is necessary to assume that this substance is unstable and breaks down gradually when the muscle is injured: its amount may then be deduced from the increase in inorganic phosphate between two moments, one immediately after and the other an hour or two after, mincing the muscle. The evidence is somewhat indirect and the supposed rôle of hexose diphosphate as the immediate precursor of lactic acid requires wider and more direct verification. There is no doubt of the importance of phosphate in the lactic acid cycle: apart altogether from Embden's experiments Meyerhof has shown that considerably higher lactic acid yields can be obtained from minced muscles, in the presence of phosphate buffers, than in any other way. In view, however, of the definite proof by Meyerhof (confirmed in Hopkins's laboratory) that lactic acid is formed at the expense of glycogen, it is impossible to suppose that hexose diphosphate is other than an intermediary, in which case it is not easy to see why the formation of the end product should diminish the amount of the intermediary so long as the ultimate precursor is still present. Clearly much more work must be done before we understand the rôle of phosphate in the carbohydrate changes of muscle.

THE NEUTRALISATION OF ACID IN MUSCLE

The increase of hydrogen ion concentration in muscle, even in rigor or extreme fatigue, is comparatively small. At no moment during a short tetanus can an electrode stuck deep into the muscle substance detect any appreciable rise: only after prolonged stimulation does a measurable change occur. It is clear that the lactic acid which is formed is rapidly and completely neutralised, and that if it acts in producing contraction by virtue of its hydrogen

ion, then that action must be local and transient, not general and permanent. The muscle is a highly organised structure, and to compare the effect of acid bathing a complete muscle (as some have done) with its action in the living organised mechanism, is about as logical as to compare the effect of petrol poured over a motor car with its action in the engine. The lactic acid, locally produced during activity, may cause a local effect resulting in the mechanical response: that effect, however, is only fleeting, and is rapidly succeeded by the neutralisation of the acid and the relaxation of the muscle.

The nature of this neutralisation is a very interesting and important matter. As Meyerhof has shown, the total amount of alkaline salts (bicarbonate and phosphate) present in a frog's muscle is inadequate to account for the large amount of acid known to be neutralised in severe fatigue. Moreover the rise of hydrogen ion concentration and the evolution of CO_2, if neutralisation by bicarbonate were the case, would be greater than are actually observed. It is necessary to suppose that some more effective buffer, something analogous to the haemoglobin of blood, is present in muscle, and strong evidence exists for the hypothesis of a sodium (or potassium) compound of protein, capable of neutralising acid according to the scheme:—

$$\underset{\text{(sodium protein)}}{Na^+ + P^-} + \underset{\text{(lactic acid)}}{H^+ + L^-} \rightarrow \underset{\text{(sodium lactate)}}{Na^+ + L^-} + \underset{\text{(protein)}}{HP}$$

This protein is a weaker acid than H_2CO_3 or NaH_2PO_4 and it acts as the first line of defence against a rise of hydrogen ion concentration. The substance in question has not yet been isolated from muscle: the evidence for its existence is indirect: it is impossible, however, to explain the facts if we deny its presence.

SELF-INHIBITION OF BREAKDOWN

The formation of lactic acid does not proceed until all the glycogen has disappeared: it stops short at a much

earlier stage. If the muscle be suspended in a solution maintained alkaline with phosphate buffers the breakdown can be pushed much further, and it is necessary to suppose that it is limited by the rise of hydrogen ion concentration and by the lack of available phosphates. The process is not yet clear, the presence of an excess both of alkali and of phosphate seems necessary in order to continue the breakdown. It is natural to connect the necessity of phosphate with Embden's hexose phosphate, but in what precise way remains to be determined: the necessity of alkali suggests other reactions which are "self-inhibited" by their resulting rise in hydrogen ion concentration. It is clear, in any case, that the lactic acid maximum and the extent of the breakdown are not determined simply by the amount of the lactic acid precursor, but rather by factors connected with the accumulation of the products of activity.

TOTAL ENERGY OF THE ANAEROBIC PROCESS

It seemed possible, although no chemical changes have ever been detected during muscular activity other than those described, that this was due rather to the failure of our means of detection than to their non-occurrence. Considerations of energy, however, negative this possibility. The total energy available in the formation of sodium lactate from dissolved glycogen may be calculated from the heats of combustion of glycogen and lactic acid and the heat of neutralisation of the latter. The heat of combustion of dissolved lactic acid is 3601 calories (Meyerhof). The older determinations of the heat of combustion of glycogen are seriously in error. A recent estimate by Slater places it at 3836 calories, for the dissolved hydrate $(C_6O_{12}O_6)_n$. Slater used the glycogen of *mytilus*, giving an ultimate analysis corresponding accurately to the above formula, and complete freedom from ash. This value is disputed by Meyerhof, whose determinations give a mean

value 46 calories less. Meyerhof's substance, however, contained 1.3 per cent of ash, irremovable by prolonged dialysis, whose combination (in some unknown form) with the glycogen may have led to some unknown heat change; it seems better to accept Slater's value. The total energy therefore, in the formation of 1 gram of lactic acid from glycogen is 3836 – 3601 = 235 calories. To this must be added the heat of its neutralisation by alkaline protein salts, which according to Meyerhof amounts to 135 calories. The total, therefore, in the formation of sodium lactate, is 370 calories per gram of hydrated glycogen broken down. This is precisely the amount found in the formation of 1 gram of lactic acid in muscle, so that, if any other chemical reactions do actually occur, their total heat-production must be *nil*. It is unlikely, therefore, that reactions of any importance arise, in the complete anaerobic cycle, other than those already known.

THE CHEMISTRY OF THE MECHANICAL RESPONSE

If the formation of lactic acid from glycogen, and its subsequent neutralisation, be the only processes involved in the complete cycle of anaerobic activity, then we must inquire how these processes can evoke the mechanical response. We have spoken of the *complete* cycle: it is obvious that in the partial cycle of contraction (i.e., in the *development of* the mechanical response) other reactions must occur, which are reversed in *relaxation:* they cannot be examined by ordinary chemical means, since they are reversed so rapidly. Presumably the liberation of acid is highly localised, and produces a large local effect on certain elements or structures (Meyerhof's "Verkürzungsorten"), evoking the mechanical response. The resulting condition, however, is unstable for several reasons, and rapidly passes off:

(*A*) The acid is free to diffuse away into the spaces of the muscle fibre.
(*B*) There, waiting for it, is an abundant supply of alkali ready to complete its neutralisation.

(*C*) The system possesses a large amount of free potential energy, which acts as a "driving force" tending to cause the reaction to be reversed.

Of these (*C*) requires further explanation. Usually in chemical reactions we do not consider mechanical energy as affecting the conditions of equilibrium: in the laboratory the case is comparatively rare. If, however, a chemical reaction goes on with the liberation of mechanical potential energy, if, for example, the pressure in a system rises as the result of a reaction, then the rise of pressure, the accumulation of potential energy, like that of any of the products of the reaction, must necessarily hinder its continuance, tend to cause its reversal. Given a suitable other path of reaction for the bodies concerned, involving a smaller accumulation of potential energy, that other path will tend to be taken. In the muscle, that other path is the neutralisation of the acid.

Unfortunately we have, at present, only the vaguest ideas as to the nature of the reactions which occur in contraction and are reversed in relaxation. There is a liberation of heat in contraction, amounting to about 60 per cent of the total initial heat, i.e., to 176 calories: in addition to this there is the appearance of mechanical potential energy. There is a liberation of heat in relaxation amounting to about 40 per cent of the total initial heat, i.e., to about 118 calories: in addition the mechanical energy disappears. It is natural to suppose that this mechanical potential energy, if unused to do external work, is degraded into heat in relaxation: the relaxation heat might represent this dissipated potential energy. This, however, is not necessary. It would be much easier to explain some of Fenn's results if we could believe that the muscle is able to reabsorb such of its mechanical potential energy as remains after doing external work. Fenn found an extra liberation of energy, if work is done, in amount approximately equal to the work. If we could suppose that

potential energy transformed into work cannot be reabsorbed while potential energy not so transformed can, we should have an explanation of the most important of Fenn's results. Unfortunately, such a simple theory will not explain why shortening during relaxation causes a diminished, and not an increased, production of heat. Fenn has provided us with some very difficult problems.

Finally, for a long period after the contraction is over, there is a delayed anaerobic production of heat, amounting to about 74 calories (fig. 1). That also is difficult to

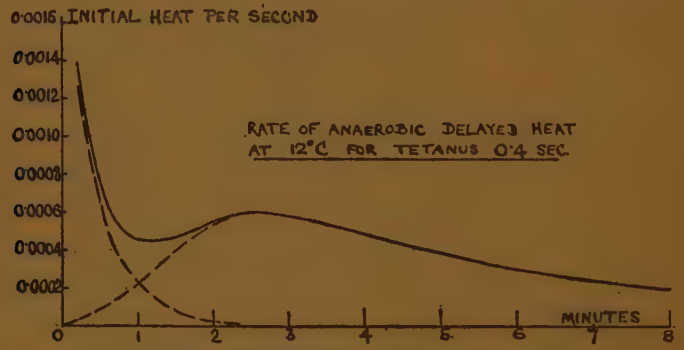

FIG. 1. COURSE OF THE DELAYED ANAEROBIC HEAT-PRODUCTION IN MUSCLE, SHOWING THE CHARACTERISTIC SECONDARY RISE IN THE CURVE WHEN THE TIME OF STIMULUS IS NOT VERY SHORT

The dotted curves represent two hypothetical simple curves making up the more complex actual one. In many cases the curve is similar to the second dotted one. The second curve provides nearly the whole of the delayed anaerobic heat. (Hartree and Hill, 1923).

explain, unless we suppose with Slater that it represents the continued neutralisation of the acid, or rather the slow replacement of an initial local neutralisation with alkaline salt by a final general and more permanent neutralisation with sodium protein. The latter yields more heat and probably more free energy than the former, so that such a replacement might well occur. Relaxation may result from a rapid neutralisation of the acid, by any alkalies available in the locality of its appearance:

the anaerobic delayed heat may represent the change over from the temporary and local to the permanent and general condition of neutralisation. Unfortunately the subdivision of the complete anaerobic cycle into its several stages is little but speculation, aided by a very imperfect thermodynamic outline. Chemists must invent far finer and more rapidly reacting tools before they can hope to get inside the mechanism, and to examine anything but the initial and final products of activity. Perhaps light may come from a chemical examination of some much slower form of movement, occurring in some other cell or organism.

THE CHEMICAL PROCESSES OCCURRING IN THE PRESENCE OF OXYGEN

In a resting isolated muscle left in oxygen lactic acid does not appear: any originally there tends to disappear. In an isolated muscle stimulated in oxygen lactic acid is set free, but vanishes again during a subsequent resting period. During this "recovery process" so-called, CO_2 is produced equivalent in amount to the oxygen used, heat is liberated, and glycogen is restored. The amount of glycogen gained is not equivalent to the lactic acid lost: a certain amount of one or the other is oxidised, presumably to provide the energy to drive the endothermic reaction:

Sodium-lactate + protein→sodium-protein + glycogen

According to Meyerhof, about 1 molecule in 4 of the lactic acid removed in recovery is oxidised, the remaining three molecules reappearing as glycogen.

In any attempt to follow, by direct chemical estimations in the isolated muscle, the reactions of recovery, the fundamental difficulty occurs that, owing to the relatively large errors of the chemical measurements involved, considerable changes must be studied. The muscle must be violently fatigued, considerable quantities of lactic acid

must be produced and removed, large quantities of glycogen must be restored. Now severe fatigue in the intact muscle may be rapidly recovered from, as is seen in the case of man after violent exercise: the rapidity is due to the plentiful supply of oxygen through the circulation. The study of the fundamental changes, however, must be made in the isolated muscle, since we cannot say how much lactic acid may be removed, or how much glycogen brought or carried away, by the circulating blood. In the isolated muscle, unfortunately, the oxygen supply has to depend on diffusion and is very poor, so that recovery from severe fatigue is extremely slow, the condition of the muscle is abnormal and the usual relations of recovery may be distorted. For this reason the myothermic method, by reason of its great sensitivity, yields more consistent and reliable results.

In an isolated muscle in oxygen, there is ample oxygen dissolved in the muscle itself to complete the recovery from a short stimulus. A tetanus of 0.1 second produces, at 20°C., an immediate rise of temperature of about 0.02°C.: the complete cycle, therefore, of breakdown and recovery causes the evolution of about 0.05 calories per gram of muscle, which requires about 0.01 cc. of oxygen. The solubility in water of damp oxygen (at 1 atmosphere pressure) at 20°C. is 0.030, in muscle therefore about 0.025, so that about $2\frac{1}{2}$ times as much oxygen is present, ready dissolved and immediately available, as is required in recovery from 0.1 second tetanus at 20°C. Thus recovery after such a short interval of activity can go on at a rate entirely independent of the oxygen supply, presumably therefore at least as well as in the normal muscle with its circulation intact. In such a muscle the heat-production may be studied, its total amount determined, its time-course plotted out, with the following results:

(*a*) The total heat liberated in the complete cycle in oxygen is almost exactly twice the total heat of the partial cycle without oxygen:

(*b*) The delayed oxidative heat production follows a complicated curve, rising rapidly to a maximum and falling slowly to zero again:

(*c*) The speed of the recovery process increases rapidly as the temperature rises, decreases as the temperature falls:

(*d*) The speed of the recovery process is affected by the hydrogen ion concentration, being greater in an alkaline, less in an acid medium.

The total heat in the absence of oxygen is 370 calories per gram of lactic acid set free. In the reversal, therefore, of the reactions of anaerobic activity 370 calories of energy must be absorbed. In oxidative recovery, however, about 370 calories of heat appear, so that a total of 740 calories of energy must have been liberated, 370 as heat, 370 as the chemical energy of the glycogen + sodium-protein restored. The net result of the whole process, breakdown followed by complete recovery, is that a certain amount (x grams) of glycogen has disappeared by oxidation, and 740 calories of heat have been evolved. Everything else has returned, so far as we know, to its initial condition, so that $x \times 3836$ (the heat of combustion of glycogen) must equal 740; hence $x = 1/5.2$; 5.2 molecules of lactic acid have disappeared for every one oxidised. The precision with which this estimate can be made, the good condition of the experimental muscle, and the normality of its recovery conditions, make it clear that this estimate is not far from the truth. As a matter of fact, practically the same value is reached by experiments made on man, as will be described in my next lecture.

The speed of the recovery process, in the presence of adequate oxygen, is clearly determined by chemical reactions: so much is shown by its high temperature coefficient. In the isolated muscle the substance oxidised is carbohydrate or lactic acid of the same empirical formula: so much is shown by the respiratory quotient. In man, practically

any respiratory quotient within the range from 0.71 to 1.00 may be observed during continued muscular exercise: the complete cycle, however, of exercise and recovery, in the case of a short interval of exercise, has been shown to have a respiratory quotient of unity, and involves therefore only the oxidation of carbohydrate. If the exercise be prolonged, fat is apparently transformed to reinstate the carbohydrate used: the *primary* fuel, however, of the muscle is carbohydrate. The matter will be discussed more fully in my next lecture, but experiments on man have fully confirmed Meyerhof's observation on the isolated muscle, that carbohydrate only is oxidised in recovery.

How then are we to regard the recovery process? May we think of the

$$\text{glycogen} \rightleftarrows \text{lactic acid}$$

mechanism as entirely distinct from the oxidative process in which energy is liberated to drive the reaction to the left? May we regard the breakdown and restoration as occurring in a separate system, analogous to a lead accumulator, having no connection with the oxidative reaction which provides energy to drive the dynamo—so to speak—by which the restoration is effected? Or should we consider some type of complex "coupled" reaction, represented empirically by the formula:

$$5C_3H_6O_3 + 3O_2 \rightarrow \frac{2}{n}(C_6H_{12}O_6)_n + 3CO_2 + 3H_2O$$

It is impossible at present to say. The decision is one of the major problems of the science of carbohydrate metabolism: we can only indicate the problem now.

The effect of a rise of hydrogen ion concentration in diminishing the speed of the recovery process was not altogether unexpected. Other oxidations analogous to those occurring in living cells are similarly affected, e.g., the autoxidation of cystein or glutathione. It is striking that the effect of CO_2 in this respect is considerably greater

than that of a corresponding change in the hydrogen ion concentration of a fluid bathing the muscle: the explanation of this may well be that CO_2 produces its effect by its greater capacity for penetrating the walls of the muscle cell, a property established by Jacobs on other cells. The effect of cyanide on the recovery process is to inhibit it completely, as in other oxidative systems.

THE REGULATION OF THE SUPPLY OF ENERGY

When a muscle is stimulated with a tetanising current the ratio of the heat-production to the force developed and maintained is practically a linear function of the duration of the stimulus (p. 43).

$$\frac{H}{Tl} = A + Bt$$

where H is heat-production, T is force, l is length of muscle, t is duration of stimulus. A and B are constants. A is independent of the temperature, having a value always about 1/5.5, B increases rapidly as the temperature is raised. This relation was expected. A rise of temperature quickens the twitch, diminishes its scale of time so to speak: and a tetanus, which is a fusion of twitches, should have the same heat-production in a shorter time, or a greater heat production in unit time. This relation, therefore, is intelligible on general principles.

If, however, we consider how the heat-production—not its ratio to the force developed—varies with the time, we find a relation which is not strictly linear, but which becomes linear after a short interval (fig. 2). Heat is liberated continuously at a constant rate as the stimulus is prolonged. There is, so to speak, a steady stream of energy outwards, and nothing that one can do—save raise the temperature—can increase that stream. Increase the strength of the tetanising current, increase the frequency of stimulation, and the rate of heat production during a

prolonged contraction remains the same. There is clearly some path of limited dimensions down which must pour the stream which represents the conversion of glycogen into

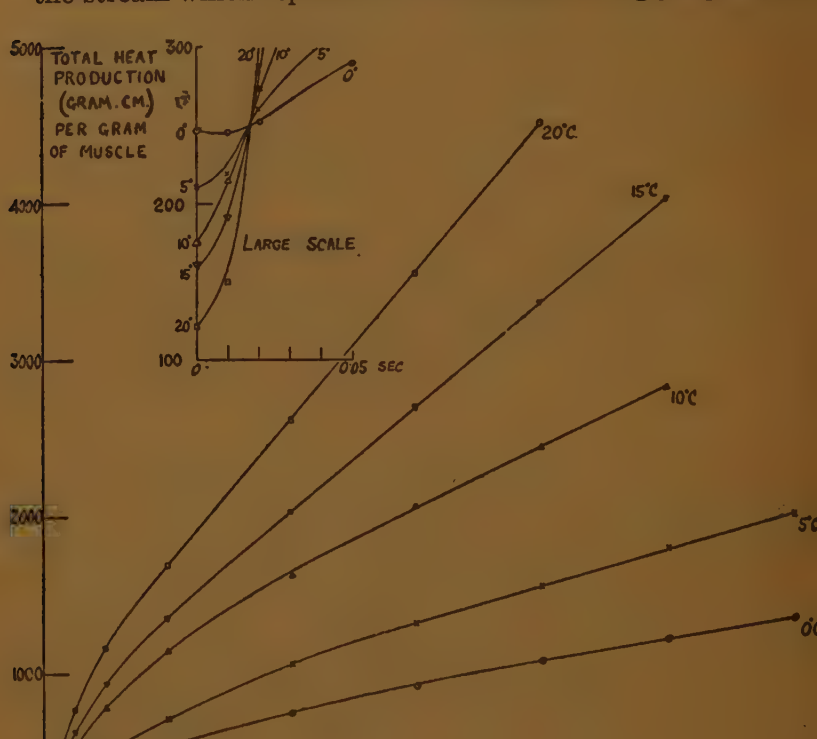

FIG. 2. RELATION BETWEEN HEAT-PRODUCTION, DURATION OF STIMULUS AND TEMPERATURE

The large diagram shows the curves up to 2 seconds on a small scale; the small diagram shows the initial shape of the curves up to 0.05 second on ten times the scale. Actual observations shown by dots. (Hartree and Hill, 1921.)

sodium lactate: that path presumably is a chemical one since it is widened by a rise of temperature. Were the rate at which energy can be liberated dependent simply

on the permeability of a membrane to certain chemical bodies, a temporary rise in permeability being effected by each stimulus, then the rate should not be much increased by a rise of temperature. It would seem rather that the reactions released by stimulation have to pass along a certain chemical channel of limited dimensions, limited that is to say by the amount of certain intermediaries or katalysts available. Each stimulus causes a momentary opening of the channel, stimuli applied with a sufficient frequency to obtain muscular summation leave it open for a sufficient proportion of the time to allow all the energy to escape which can escape. A rise of temperature widens the chemical channel, diminishes the scale of time, and allows the energy to escape more rapidly. The rate of heat liberation during a prolonged stimulus rises as an exponential function of the temperature, it has the usual type of temperature coefficient.

What the reactions may be which regulate the speed at which energy is liberated by muscle we do not know. Glycogen dissolved in water does not, of itself, change into lactic acid: presumably the reaction must proceed by virtue of some agency which—because of our ignorance—we describe as a katalyst. In an enzyme action, under certain circumstances, the speed may depend, not so much on the concentration of the reacting bodies as on the amount of enzyme present. So, in muscle, the speed of the transformation of glycogen to lactic acid may depend upon the amount of certain agencies or bodies which assist the reaction.

There is still another clue available in the thermodynamic relationships. During the initial outburst of heat following the commencement of the stimulus the rate of heat-production is far greater than it is finally during the steady state. The speed of the liberation of energy, and presumably of lactic acid, is very rapid at first and tails off gradually to its final constant value. It is clear that our analogy of

a channel along which the reaction can proceed is not complete: there must in addition be some quite considerable store of energy immediately available which has already passed—so to speak—through the channel, which is released—without further ado—as the stimulus commences. Stop the stimulus, block the output, and the store is replenished ready for the next shock. It is tempting to suppose that there is a "ready-store" of some intermediate body, e.g., of hexose-diphosphate, intermediate between glycogen and lactic acid. This "ready-store" is thrown into action by the stimulus, and is released at a high speed; as soon as it begins to be depleted the process of restoration gets under way, and glycogen is broken down to reform the intermediary: during prolonged anaerobic stimulation the rate of release is balanced—indeed is determined—by the speed of restoration. These processes we cannot at present define, but that some such processes occur is made certain by the thermodynamic outline of prolonged stimulation.

THE RELEASE OF ENERGY

When a stimulus is applied some kind of door is opened, energy is released, lactic acid is set free. In a prolonged stimulation the rate of the release is determined by the rate at which the ready store of energy can be refilled. In a single twitch, with a ready store of energy several times exceeding the total amount required, the rate of restoration does not affect the result: the energy set free during a twitch depends, rather, on the duration and degree of the opening of the door. To adopt a more definite picture, a shock causes a momentary change in the permeability of some membrane, which normally restrains chemical bodies, whose escape results in the reactions, which end in the formation of lactic acid and in the mechanical response. The duration and degree of this change in permeability are determined by a variety of factors. Normally, even

at rest, there is production of lactic acid and heat, presumably the impermeability is not absolute. The degree of permeability—small though it be—determines the basal metabolism of the muscle. In a twitch the permeability rapidly rises and rapidly falls: perhaps its cycle of changes is an accompaniment of the action current. The output of energy in the twitch depends upon the duration of its alteration. It was likely that this rise of permeability would prove to be more prolonged at a lower temperature, so allowing time for more energy to escape. This expectation was confirmed by the observation that the heat-production in a single twitch is greater at a lower temperature. In a prolonged stimulation the heat-production is greater at the higher temperature, and it is difficult to explain the opposite effect for a twitch except on some such lines as these.

Again, stretching a muscle initially causes a more prolonged contraction, a greater heat production. If, as Fulton emphasises, lactic acid is freed by a wave of permeability passing along a polarised membrane, permitting in consequence the reactions of the intermediary body present in the "ready store," the duration of the wave at any one point will determine the amount of lactic acid produced. It is very suggestive that the "chronaxie" of muscle is found to increase with tension, as is that of nerve. Curare, also, according to the Lapicques, increases the chronaxie of muscle, thus rendering it unstimulable by its usual nerve impulse. Hartree and I found that curare increases the heat production of a muscle responding to a single shock, and suggested that curare may prolong the rise of permeability following the stimulus. Curare also prolongs the twitch, much as does an increase in the initial tension. All of which confirms our view that, in a twitch, the amount of energy released depends upon the duration of the primary effect—a change of permeability or whatever it may be—of a shock.

Other factors influence the release of energy. In a muscle treated with veratrine, about 0.002 per cent, there

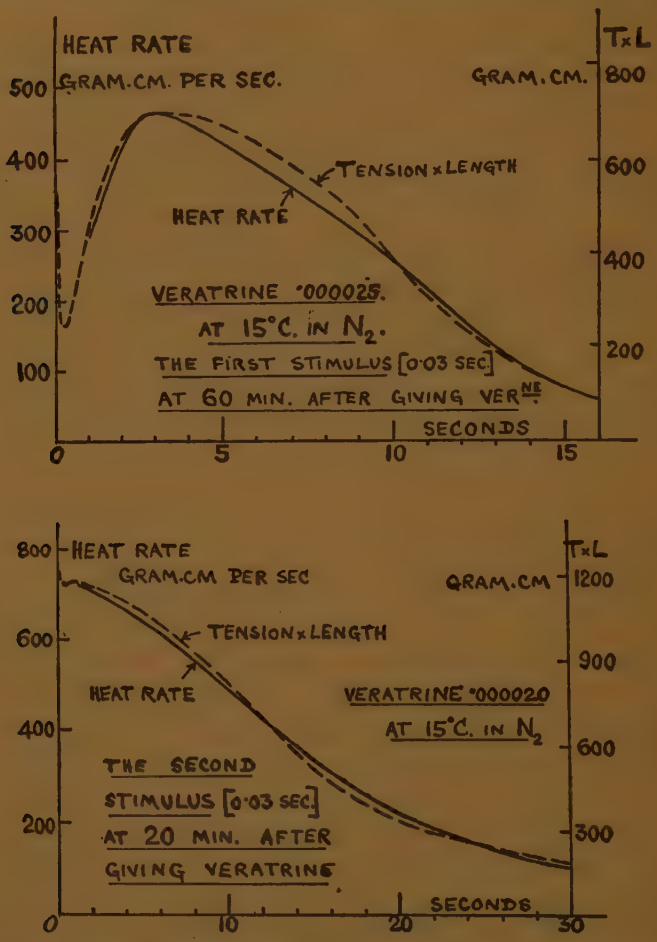

FIG. 3. RELATION BETWEEN FORCE MAINTAINED AND RATE OF HEAT-PRODUCTION IN A VERATRINE CONTRACTION

(Hartree and Hill, 1922)

is a prolonged liberation of heat accompanying the prolonged contraction resulting from a single shock (fig. 3). The rate of liberation of heat runs exactly parallel to the

force maintained—so much tension, so much heat-production per second: and not only that, but the relation of heat-production to tension is precisely the same as in normal tetanised muscle. There is no truth whatever in the conception that veratrine has its effect by delaying relaxation: it works by affecting the duration of the liberation of energy following a shock. In the normal muscle there is some "passage" of escape for the energy and lactic acid, which is opened by a shock and then rapidly closes again. In a muscle subjected to a large dose of veratrine the instability of the galvanometer zero shows that the passage is so nearly open that small spontaneous outbursts occur. With a weaker dose, the "passage," once opened by a shock, remains open for some time, allowing considerable quantities of lactic acid to pour out, with a prolonged maintenance of tension and a prolonged production of heat. The effect of veratrine may be largely antagonised by Ca salts, from which it may be argued that its action lies in a change produced in some membrane. However that may be, there is no doubt of the existence of some mechanism regulating the duration of the release of energy, and of the action of veratrine thereon.

Again, caffein applied to a muscle gradually causes a state of contracture, a liberation of heat, a production of lactic acid (fig. 4). The rate at which these processes develop does not depend upon the gradual diffusion of caffein into the muscle substance. A few minutes subjection to a dilute solution of the drug is enough, and after that, in a period of several hours, the release of energy occurs. The same total amount of energy may be liberated, either in oxygen or in nitrogen, by discontinuous stimulation over the same period, instead of subjection to caffein (fig. 5). The action of caffein on muscle is merely to release, slowly and continuously, the chemical processes, anaerobic or oxidative, normally induced, suddenly and discontinuously, by stimulation. Presumably, therefore,

in terms of our permeability hypothesis, the action of caffein is to induce a permanent and slight impairment of the resting impermeability of the membranes, which normally restrain the reactions producing activity in muscle.

Still a simpler case may be considered: the complete removal of Ca and K from the fluid bathing a muscle often causes after a shock (at any rate in *Rana temporaria*), a prolonged contracture not unlike a weak veratrine con-

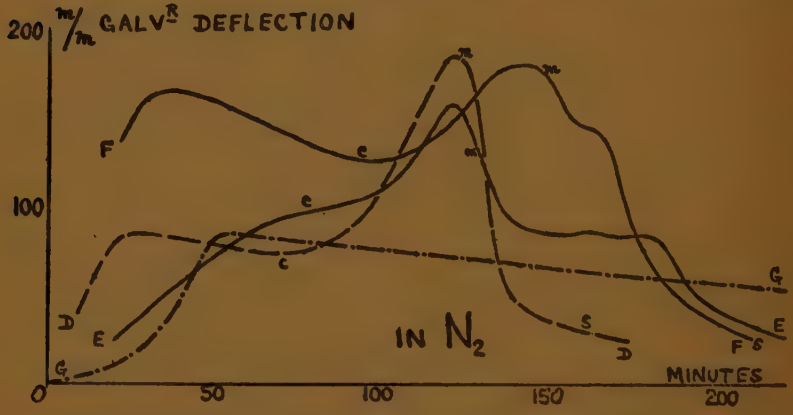

FIG. 4. HEAT-PRODUCTION (GALVANOMETER DEFLECTION) IN MUSCLE IN NITROGEN, AFTER TREATMENT WITH 0.050 TO 0.075 PER CENT CAFFEIN

(Hartree and Hill, 1924)

traction. Here again the total heat-production is increased, here again an analysis of the heat-production shows it to be protracted throughout the prolonged response. The absence of Ca and K results in a prolongation of the interval of altered permeability.

MOLECULAR AND THERMODYNAMIC THEORY

The argument has been advanced that muscular contraction must be due to surface action, since the force

developed in a twitch diminishes with a rise of temperature —which is what surface tension does. This argument is invalid. The relation of tension to heat production in a twitch is *independent of temperature*, a given liberation of lactic acid produces, at all temperatures, the same rise of tension. The system, moreover, is certainly never in a

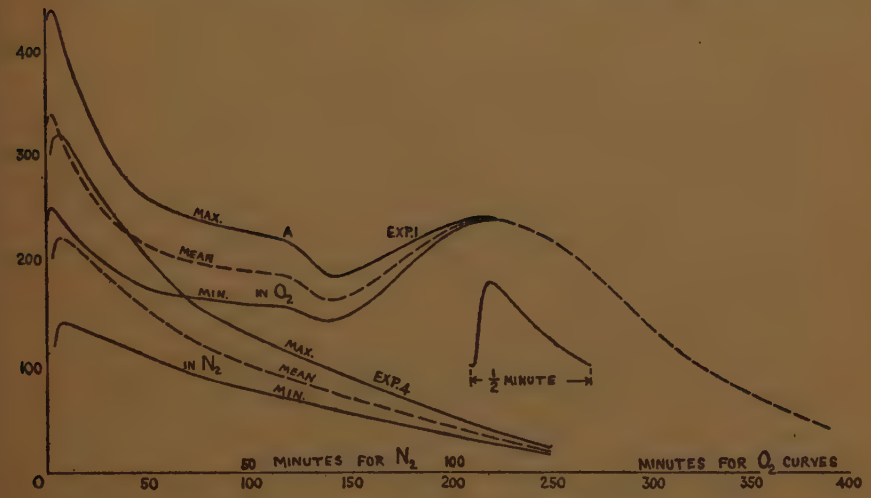

FIG. 5. HEAT-PRODUCTION (GALVANOMETER DEFLECTION) IN MUSCLE EXCITED DISCONTINUOUSLY TO COMPLETE FATIGUE BY A LONG SUCCESSION OF SHORT TETANIC STIMULI EVERY HALF MINUTE

The scale of time is twice as great in the nitrogen experiment. Each stimulus causes a deflection of the type shown in the small diagram inset; in each experiment the upper curve ("max.") is drawn through the tops of the successive deflections, the lower curve ("min.") through their bottoms, the middle curve ("mean") approximately half way between the other two. (Hartree and Hill, 1924.)

state of reversible equilibrium; hence no such thermodynamic arguments can be applied. It was possible, nevertheless, in spite of the fallacy of this reasoning, that a change in surface tension was the cause of the muscular response. The following calculation shows that this is quite definitely not the case.

A change in surface tension, if it is to cause the observed mechanical effect, must be produced by the lactic acid—the only substance known to be formed; and that substance must presumably be spread upon the surface where it acts, as a layer not less than one molecule thick. A most interesting calculation results. In the twitch of a striated muscle the ratio H/Tl (where H is heat-production (measured in ergs), T is force developed in dynes, l is length in centimetres), is fairly accurately about 1/5.5. The amount of lactic acid liberated, per calorie, in the *initial* anaerobic process is 1/296 = 0.0034 gram, since 370 calories per gram of lactic acid are produced in the *total* anaerobic process, and of this 1/5 is delayed. Thus, per erg of heat liberated, the amount of lactic acid formed is

$$0.0034/4.18 \times 10^{7} = 8.1 \times 10^{-11} \text{ grams}$$

Now, to produce a force of one dyne in one centimetre length of muscle, the initial anaerobic heat-production, as shown above, must be 1/5.5 erg, accompanying which must be the formation of $\frac{8.1}{5.5} \times 10^{-11} = 1.47 \times 10^{-11}$ grams of lactic acid. Now one atom of hydrogen weighs 1.66×10^{-24} grams, one molecule therefore of lactic acid $90 \times 1.66 \times 10^{-24} = 1.49 \times 10^{-22}$ grams. Thus almost exactly 10^{11} molecules of lactic acid are required to cause the development of a tension of 1 dyne in 1 cm. length of muscle. So far we are on certain ground, direct calculation from fairly exact experimental facts. Let us advance further by the hypothesis that this lactic acid is spread out in a layer one molecule thick.

The density of lactic acid in mass is 1.25 at 15°C.: let us attribute the same density to the lactic acid molecule. Its volume then will be $1.49/1.25 \times 10^{-22} = 1.19 \times 10^{-22}$ cc. Let us imagine, for simplicity of calculation, that the molecule is cubical in shape: then the area of one of its

faces[2] is $(1.19 \times 10^{-22})^{2/3} = 2.42 \times 10^{-15}$ sq. cm. Hence 10^{11} molecules would occupy an area of 2.42×10^{-4} sq. cm. Now, by hypothesis, our muscle is 1 cm. long exerting a force of one dyne. If that force be due to surface tension the surface energy of the film causing it is 1 dyne $\times$ 1 cm. = 1 erg. But the energy of any surface is:

(coefficient of surface tension) (area of surface)

and since the latter has been calculated as 2.42×10^{-4} sq. cm., the coefficient required is $\frac{1}{2.42 \times 10^{-4}} = 4100$ dynes per centimetre. Hence, on the hypothesis that our lactic acid forms a monomolecular layer, the rise of surface tension produced by it must be 4100 dynes per centimetre. This is about 55 times the surface tension of water, 178 times the surface tension of alcohol, $7\frac{1}{2}$ times the surface tension even of mercury: clearly quite an impossible quantity.

It is obviously unreasonable, therefore, to regard a monomolecular layer of lactic acid as causing a change in surface tension large enough to explain the actual force developed by a muscle. With a layer thicker than a monomolecular one the difficulty is only enhanced. It is hard to imagine a change to occur in surface tension much larger than that between water and paraffin oil, say 50 dynes per centimetre. To obtain the requisite surface energy we must then distribute our lactic acid molecules until only about *one eightieth part of the whole surface is occupied by them.* It is difficult—indeed impossible—to suppose that a change in surface tension, as large as 50 dynes per centimetres, could be caused by molecules of lactic acid dotted at such wide intervals about the surface. Clearly the surface tension hypothesis involves us in grave perplexities.

[2] Just the same area for the cross section of a fatty acid molecule, floating on water in a monomolecular layer, is given by the experiments of N. K. Adam.

It may be objected that we are not justified in assuming that lactic acid is the body which produces the surface effect in question. Something must produce the effect, however, something in a layer presumably not less than one molecule thick: and if that "something" is to be the responsible agent it must be produced in the twitch in amounts considerably greater than is lactic acid. Otherwise it cannot occupy the requisite area with any reasonable coefficient of surface tension. No such body, however, is known: its existence would seem extremely improbable. If so, therefore, we may conclude that *a change in surface tension is not, and cannot possibly be, the cause of muscular contraction.*

If surface tension be not the cause we seek, it may still be possible that the mechanical effect is ultimately a surface one, and due for example to the neutralisation of an electric charge. A surface endowed with σ electrostatic units of electricity per square centimetre, in a medium of specific inductive capacity K, is subject to an electrostatic "pressure," acting outwards of $\frac{2\pi\sigma^2}{K}$ dynes per unit of area. With σ unity this "pressure," in water with $K = 81$, amounts to 0.078 dynes per square centimetre: with $\sigma = 10$ it amounts to 7.8. Now 10^{11} ions carry $10^{11} \times 4.77 \times 10^{-10} = 47.7$ electrostatic units of charge, so that if the whole of the charge were disposed in an area of 1 sq. cm. it would lead to a "pressure" of 178 dynes per square centimetre. If it were disposed in an area smaller than 1 sq. cm. the force would be proportionally greater. It is impossible to calculate the force exerted by such a charge without knowing the details of its disposition. It is clear, however, that the total charge available in the potential ions of lactic acid, if suitably disposed, could yield forces quite adequate to explain the mechanical response of muscle.

We know that living tissues are constructed of protein

substances in the form of a combination with inorganic bodies: often these protein substances are sodium-protein salts. We suspect, moreover, that lactic acid, when formed during activity, is set free in high local concentration at surfaces from which it passes away rapidly by diffusion and neutralisation. During its sojourn in the immediate neighbourhood of the sodium-protein membranes, or surfaces of muscle fibres or fibrils, it might well cause—owing to its "mass" effect—a de-ionisation of the protein according to the scheme

$$Na^+ + P^- + H^+ + L^- \rightarrow Na^+ + L^- + HP$$

This reaction we know normally liberates a large amount of heat (Meyerhof): under other circumstances it might perhaps yield a large amount of mechanical energy. Imagine that the protein surfaces exist at rest under their own intrinsic tension, balanced by the electrostatic repulsion of their individual elements of charge. Then a sudden de-ionisation of their surface would lead to a disappearance of those electric charges and their consequent repulsion, and as in a capillary electrometer the tension manifested externally would rise: to fall again as soon as the acid had diffused away and been removed by neutralisation. In a general way this theory is not prohibited by simple numerical facts, as is that of surface tension: there may be other objections to it, and the precise nature of the reactions which result in contraction and relaxation cannot but remain, for the present, a matter of speculation.

To pry into the chemical nature of the actual processes of life is very attractive—but very hard. It is so difficult to get inside the living cell without destroying its structure and stopping its machinery. Yet we may be encouraged by the history of chemistry and physics. For long no direct evidence of any kind was forthcoming, as to the actual nature, or even the existence, of atoms, molecules and chemical structure. Their objective presence was

sometimes doubted, the theories built up around them seemed to work, but it was open to anyone to believe that these were only useful hypotheses, useful but not ultimately true. Yet of recent years the work of physicists and chemists, of Thomson, Wilson, Perrin, Rutherford and Langmuir, has given us certainty that the theories of atoms, molecules and stereochemistry, are based upon real objective fact: we can see the α-particles forming a streak of cloud: we can study the molecular impacts of Brownian movement: we can weigh, as Adam does, the repulsions of fatty acid molecules swimming on the surface of water, with their $-COOH$ groups pointing downwards. So it will be with physiology, though our way be much harder and longer than that of those who deal with such simple things as molecules, atoms and electrons.

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THE RECOVERY PROCESS AFTER EXERCISE IN MAN

FOURTH HERTER LECTURE

THE RECOVERY PROCESS AFTER EXERCISE IN MAN

LACTIC ACID IN MAN

It is a common observation that after exercise breathing is deep and rapid—that recovery is necessary. The same process must occur as in the isolated muscle, complicated in this case by the presence of the respiratory and circulatory mechanism. It can be shown, though by less direct evidence, that lactic acid occurs in human muscles as it occurs in isolated amphibian muscles. It had not been realised, however, till recently, how extensive are the changes connected with the lactic acid which is produced in the human body during exercise. When an athlete is running as fast as he can, about 4 grams of lactic acid per second are being liberated in his muscles. About 130 grams may be produced before exhaustion is complete. There are several signs of this lactic acid in the body. It occurs in the urine, though only in small amounts, after prolonged hard exercise. In the blood of a resting man there is 0.01 to 0.02 per cent; during and after severe exercise there may be as much as 0.12 per cent, or under exceptional circumstances, 0.20 per cent. This may be estimated directly by chemical analysis, or it may be inferred, as Barcroft did, from the change it produces in the oxygen dissociation curve. There is a very high respiratory quotient during, and especially just after, severe exercise (see fig. 1); in our experiments we have found values as high as 2; the lactic acid raises the hydrogen-ion concentration of tissues and blood; this stimulates the respiratory centre, with the result that CO_2 is eliminated by the lungs. In a later stage of recovery correspondingly the respiratory quotient falls to very low values as the

lactic acid is removed. It may remain for considerable periods below the value corresponding to the oxidation of fat (fig. 2). The chief sign, however, of the amount of lactic acid present in the body after exercise is the magnitude of the so-called "oxygen debt." A muscle which has been active requires oxygen to carry out the combustions needed to provide the energy for the restoration process. The oxygen used in recovery is a measure of the magni-

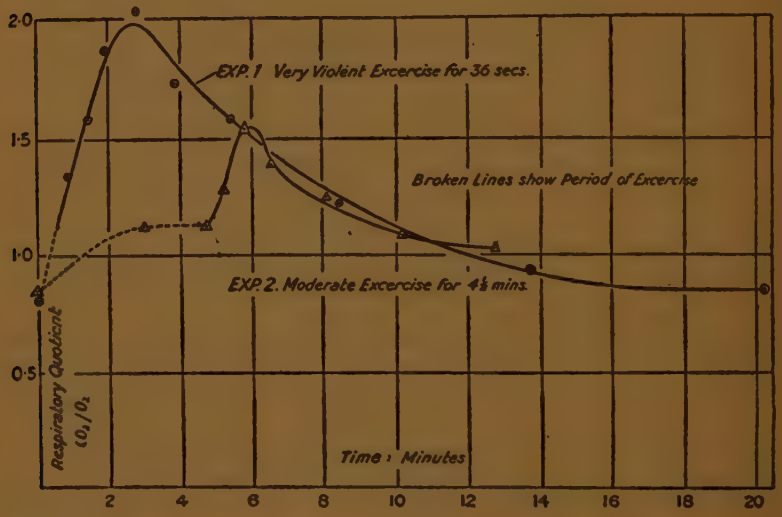

FIG. 1. THE RESPIRATORY QUOTIENT DURING AND AFTER MUSCULAR EXERCISE

These figures show the initial phase of recovery only. The final phase is shown in figure 2. (Hill, Long and Lupton, 1924.)

tude of that process—that is, of the amount of lactic acid removed. Assuming an "efficiency of recovery" of 5.2:1, 1 litre of oxygen consumed after exercise is equivalent to 7 grams of lactic acid removed. The greatest oxygen debt hitherto recorded is one of nearly 19 liters, which corresponds to a concentration of not far from 0.35 per cent in all the muscles of the subject; he was well-nigh exhausted.

The changes in the lactic acid concentration in the

blood are very instructive. During moderate continued exercise it rises, in a few minutes to a steady constant value, remaining there so long as the exercise lasts. After the exercise it returns slowly to its original value. During severe exercise it rises continually, till the exercise is stopped by distress (fig. 3). Afterwards it may continue to rise for a few minutes, by diffusion from the muscles:

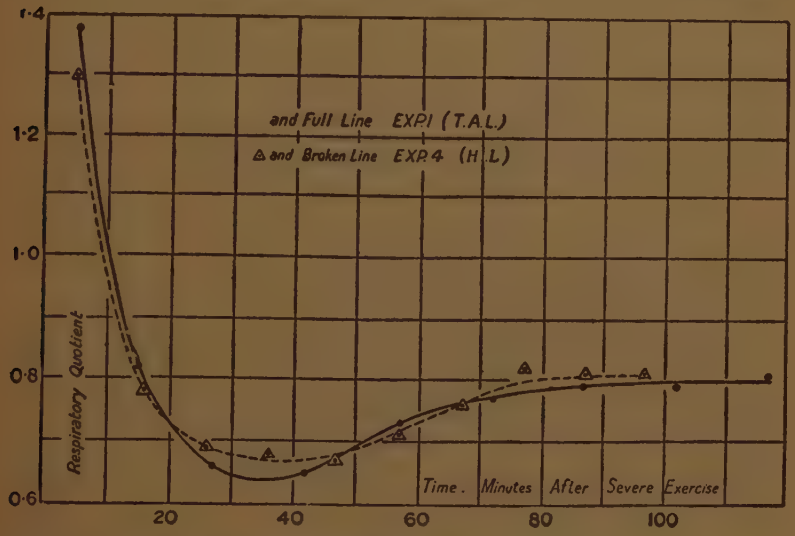

FIG. 2. THE RESPIRATORY QUOTIENT AFTER SEVERE MUSCULAR EXERCISE

Note that in the later phases, while carbon dioxide is being retained to compensate for that initially driven off, the respiratory quotient falls to a very low level, returning to its final value at about 80 minutes. (Hill, Long and Lupton, 1924.)

then it begins to return to its normal value, attaining that some time in the second hour after the exercise ended. Its changes give the same information, in another form, as is given by the changes of the respiratory quotient.

STUDIES OF OXYGEN INTAKE

The greater part, however, of our knowledge of the events occurring in human muscular exercise has been arrived at

by studies of the oxygen consumption. The measurement of oxygen intake is possible in many ways. One involves the continuous circulation of oxygen in a closed system, which includes the lungs of the subject, the CO_2 being absorbed and the diminution in volume owing to consumption of oxygen being recorded. The method is accurate

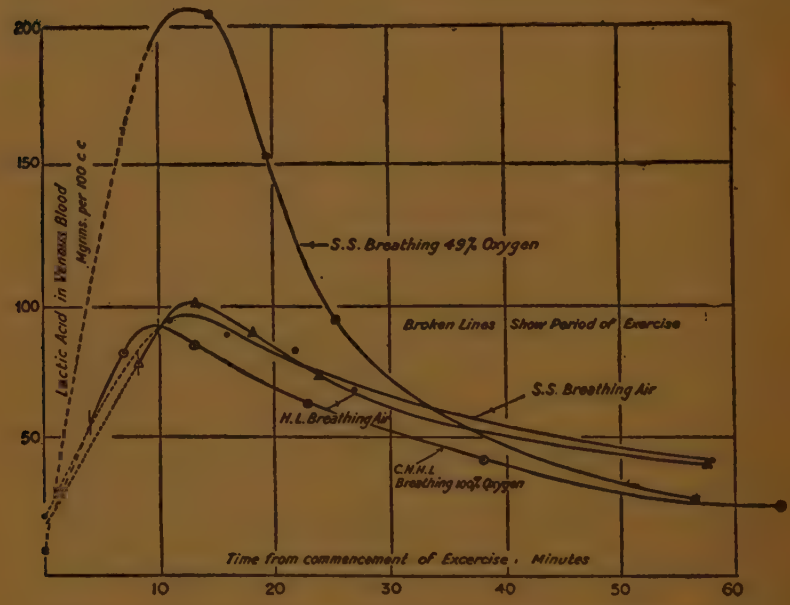

FIG. 3. LACTIC ACID IN HUMAN BLOOD AFTER SEVERE MUSCULAR EXERCISE; TWO EXPERIMENTS IN AIR, ONE IN 49 PER CENT OXYGEN, ONE IN 100 PER CENT OXYGEN

Note that the recovery process is not quite complete at the end of the time shown in the diagram. (Hill, Long and Lupton, 1924.)

but inadaptable; it is not capable of analysing the time-course of the oxygen consumption when the latter is changing rapidly, as at the beginning and end of exercise. Another method, used by Krogh and Lindhard in their recent and admirable researches, is to place the subject in a closed room of known volume, and to determine the small changes in the gas concentrations inside it by a highly

sensitive gas-analysis technique. The method is very accurate and convenient to the subject; it is elaborate, however, and—without very violent mixing of the air in the chamber—could not be used over very short intervals. For such purposes the technique of the Douglas bag, in which the subject expires into a large bag carried on his back or in front of him, and the expired gases are analysed and their volume measured, is sufficiently accurate and is capable of following very rapid changes. It is possible to use this method when walking, running, riding a bicycle, even swimming, and to plot the time course of the oxygen consumption in intervals as short as half a minute. Under certain circumstances, even quarter minute intervals may be employed.

THE "STEADY STATE"

An isolated muscle contracting in an atmosphere of oxygen rapidly attains a steady state; in such a muscle there is a balance between breakdown and recovery. In an atmosphere of nitrogen such a steady state is never attained: fatigue progressively occurs, and the muscle finally becomes inexcitable. The recovery process is more rapid when the total amount of breakdown causing it is greater; lactic acid is a sensitive "governor" of oxygen usage. Hence, if we start with a given rate of breakdown, as when a man suddenly begins to run at a given speed, the rate of recovery, starting from zero, has to work up gradually until it balances the rate of breakdown (fig. 4). It is necessary, moreover, in the intact animal, for the circulation and respiration to work up also. In a subject starting to run, having been previously at rest, the oxygen intake rises to its full steady value in a period of about two to two and a half minutes. If the running be continued at a constant speed the oxygen intake also remains constant thereafter till the end of the exercise; the subject is

in what we may call a "steady state." This state corresponds to a constant concentration of lactic acid in the muscles, constant owing to a balance between formation and removal. As the exercise, however, is continued, the

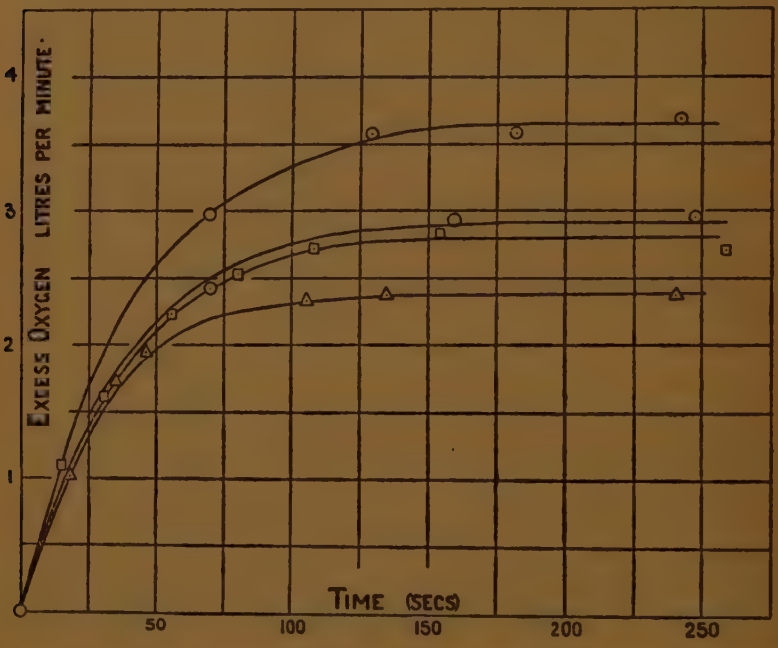

FIG. 4. THE ATTAINMENT OF A "STEADY STATE," IN RUNNING AT VARIOUS CONSTANT SPEEDS

Horizontally, time from commencing to run; vertically, rate of oxygen intake in excess of standing. Speeds of 181, 203, 203, and 267 metres per minute. The lower three curves represent a genuine steady state, the uppermost curve only an apparent steady state in which the oxygen intake is at its maximum and the "oxygen debt" is rapidly increasing. (Hill and Lupton, 1923.)

lactic acid present in the active muscles gradually passes, by diffusion, into the blood and thence to other parts of the body. This is probably one cause of the fatigue resulting from long-continued moderate exercise. The oxidative removal of the lactic acid formed in one muscle may,

in this manner, occur in other distant muscles by its passage, via the blood, from the one to the other. As Barr and Himwich have found, the venous blood from a resting muscle, during the vigorous activity of others, may contain *less* lactic acid than the arterial blood coming to it. Indeed, in this sense it is possible to recover in one's arms from exercise taken in one's legs! This may be an important factor in recovery from vigorous exercise taken by

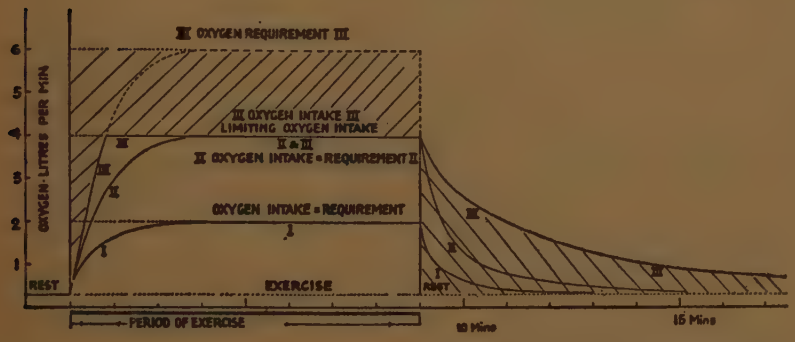

FIG. 5. DIAGRAM TO REPRESENT OXYGEN INTAKE AND OXYGEN REQUIREMENT FOR THREE DEGREES OF EXERCISE: I, MILD; II, MODERATELY SEVERE; III, VERY SEVERE

(Hill, 1924)

small portions of the muscular system; it cannot have much effect in severe general exertion.

It is to be noted that an apparent "steady state" may occur, during muscular exercise, in which the oxygen intake is constant, which is not, however, really "steady" at all; there is a continual onset of fatigue. The oxygen intake may attain its maximum and remain constant *merely because it cannot go any higher* owing to the limitations of the circulatory and respiratory system (curve III, fig. 5). Such a condition causes an accumulation of lactic acid in the muscles and can end only in complete exhaustion.

RECOVERY

When the exercise terminates the lactic acid in the muscles must be removed and oxygen must be taken in to provide the necessary energy. The lag in the oxygen intake at the beginning of exercise, during which the lactic acid was concentrating, must be compensated by an extra intake afterwards when it is diminishing again. After a short bout of moderate exercise the oxygen intake falls

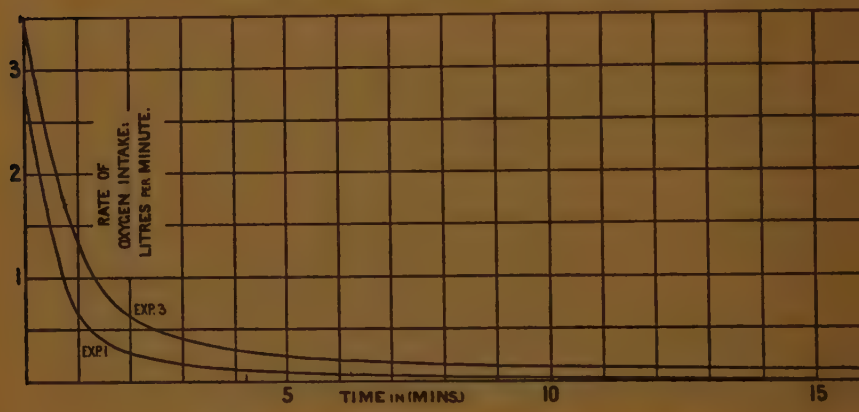

FIG. 6. OXYGEN INTAKE DURING RECOVERY

Horizontally, time from cessation of exercise; vertically, rate of oxygen intake in excess of standing. The lower curve, falling rapidly to the base line, represents recovery from a short bout of moderate exercise. The upper curve, falling less rapidly, represents recovery from a rather longer bout of much more strenuous exertion. (Hill and Lupton, 1923.)

in a period of five to ten minutes to its resting value (fig. 6). After severe or prolonged exercise it may be 80 minutes before the oxygen intake is at its resting value again (fig. 7). The total amount of oxygen used in the recovery process may be measured by collecting the whole of the expired gases over any desired interval, by an estimation of the total oxygen used in that interval, and subtraction of the amount of oxygen which the subject would have used had he remained throughout at rest.

There are apparently two phases in the recovery process. The first and rapid phase (fig. 6) involves the oxidative removal of lactic acid in the muscles where it was formed. The second and prolonged phase (fig. 7) deals with the removal of lactic acid which has had time (after severe exercise) to escape, by diffusion, from the muscles where it was liberated, into the blood and thence into all the

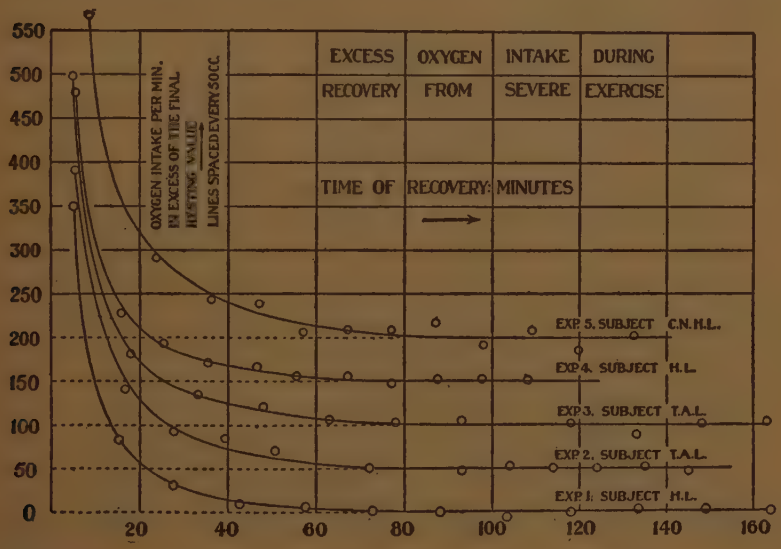

FIG. 7. RECOVERY OXYGEN INTAKE AFTER VERY SEVERE EXERCISE: FIVE EXPERIMENTS PLOTTED (FOR CLEARNESS) TO DIFFERENT BASE LINES

(Hill, Long and Lupton, 1924)

other tissues of the body. The slowness of the diffusion process makes the second phase a very prolonged one.

"OXYGEN REQUIREMENT"

It is desirable here to introduce a new term—namely, the "oxygen requirement" of exercise (fig. 8). If the exercise be mild, then the oxygen requirement may be met by the actual oxygen intake once the steady state has

been attained. If, however, the exercise be severe the oxygen requirement cannot be met, even when the heart and lungs have attained their maximum activity; if the exercise be persisted in, the body necessarily incurs what we may call an "oxygen debt." Were it not for the fact that the body is able to obtain its energy in this way, by using its necessary oxygen afterwards, severe exercise would be impossible in man. We should never be able to run upstairs, or to run on the flat at more than eight or

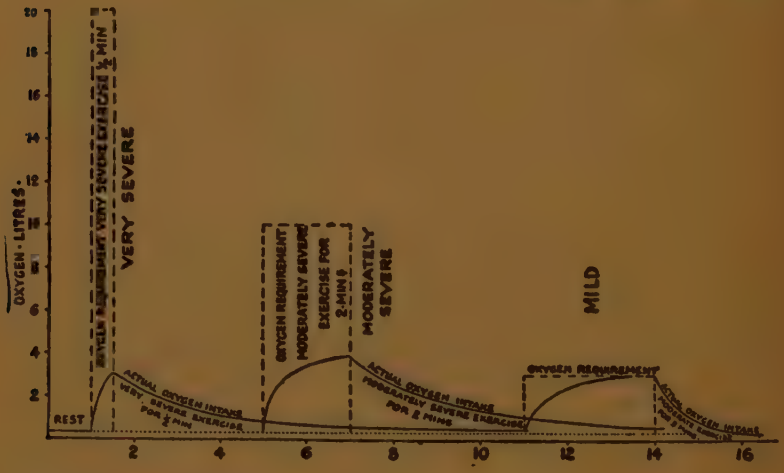

FIG. 8. DIAGRAM TO ILLUSTRATE FURTHER (CF. FIG. 5) THE OXYGEN INTAKE AND THE OXYGEN REQUIREMENT

(Hill, 1924)

nine miles an hour. We can do so only because Nature has provided us with an arrangement, like an accumulator which can be run down at a very high rate, as in starting a car, and then must be re-charged slowly afterwards.

The oxygen requirement of a given type of exercise, or of a given isolated movement or series of movements, can always be measured. The oxygen requirement may be many times higher than any possible oxygen intake. If, however, the movement be carried out only for a short

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time, and the total oxygen used *during it and in complete recovery from it*, be measured, then the total oxygen so found is the requirement of that piece of effort. In this way it is possible to study the energy requirement of even the most violent and discontinuous movements. To take an example, Lupton has measured the maximum efficiency of the process of climbing a staircase, in an endeavour to show that there exists, for many muscular movements,

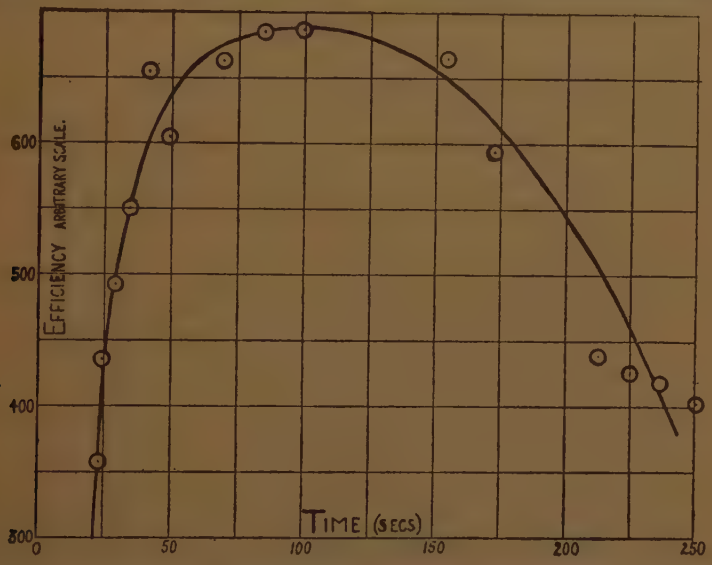

FIG. 9. "EFFICIENCY" (INVERSE OF OXYGEN REQUIREMENT) OF STAIR-CLIMBING AT DIFFERENT SPEEDS

(Lupton, 1923)

a certain optimum rate (fig. 9). The subject ascends the staircase once, at any required speed varying from very slow to extremely rapid. The oxygen used during the climb and in the succeeding 20 minutes, after subtraction of the resting value for the same time, gives the oxygen consumption produced by the exercise. This decreases at first as the speed is increased, and then increases again, showing that there is indeed an optimum speed.

This existence of an optimum speed does not occur in all types of exercise. In running (fig. 10) the oxygen requirement increases continuously as the speed increases, attaining enormous values at the highest speeds; the actual oxygen intake, however, reaches a maximum beyond which no effort can drive it. Once the oxygen requirement is larger than the oxygen intake, a steady state is no longer possible, and fatigue ensues more or less rapidly.

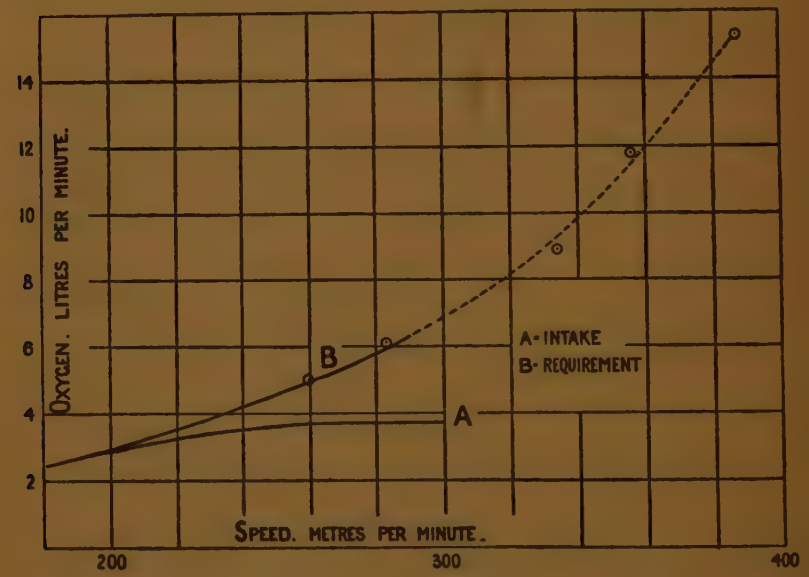

FIG. 10. OXYGEN INTAKE (*A*) AND OXYGEN REQUIREMENT (*B*) OF RUNNING AT VARIOUS SPEEDS

(Hill and Lupton, 1923)

ATHLETIC RECORDS

Some of the most consistent physiological data available are contained, not in books on physiology, not even in books on medicine, but in the world's records for running different horizontal distances. If one plots the average speed at which the record was made, against the length of the race (compressed in some manner—as by taking its logarithm—

to bring all the points on to the same diagram), then a curve of almost perfect smoothness is obtained, in which a few points only lie just below the curve (fig. 11). These latter are for the races in which athletes have not been so concerned to break the record as in the rest. The relation shown in the curve may be accepted practically as a natural constant for the human race; it would require almost a superhuman effort to change one of the points by 2 per cent; and it is interesting to consider what determines in

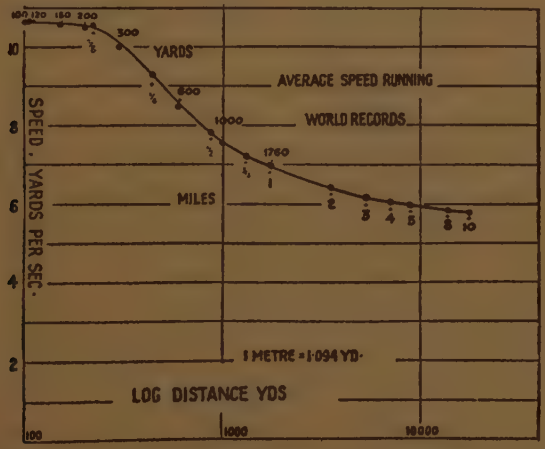

Fig. 11. World Records Running: Speed as a Function of Distance (Hill, 1924)

general the shape of this relation. At very short distances the speed is constant; it is the maximum which a man can attain, though it falls off a little as the accumulation of lactic acid in the muscles affects—first—their speed of relaxation. At very long distances the speed again tends to become constant, practically a steady state being attained. It is determined here by the maximum rate at which the athlete can take in oxygen to provide his muscles with their necessary energy, and by the economy with which he uses it. Speed at intermediate distances is determined,

partly by the maximum oxygen debt which the body can incur, partly by its maximum oxygen intake. We assume, of course, that we are dealing with a man in perfect condition, highly trained to carry out his movements in the most economical manner possible, ready and willing in a race to exhaust himself completely. In the magnitude of the oxygen debt, that is in the concentration of lactic acid which his muscles can tolerate, we have what we may regard as a man's "capital." In his oxygen intake, determined by the capacity of his heart and lungs, we have what we may regard as his "income." In a race an athlete will finish—if he can, if the race be not too short—with the whole of his reserves gone, having spent both "capital" and "income" completely. In a short race, therefore, he can spread his "capital" over a shorter time, he can expend energy more rapidly than he can in a long one; the form of the curve is determined mainly by these factors.

"OXYGEN DEBT"

Recently a number of estimations have been made of the "oxygen debt." These are small after moderate exercise—even when prolonged—large after violent exercise, even of comparatively short duration. The most striking* of the higher ones are perhaps those (*a*) in which 23 seconds of exercise led to a debt of 8.7 litres, (*b*) running for 33 minutes at a medium speed only of 7.9 litres, and (*c*) "standing running" with extreme violence for 4 minutes of 18.7 litres. The larger values mean enormous amounts of lactic acid accumulated in the body; how can this acid be tolerated? Inside the muscle are alkalies capable of neutralising the acid, and the hydrogen-ion concentration in the active muscle does not rise very far so long as the amount of these alkalies is adequate. It would seem probable that the limit to which it is possible to press a muscle

*A still more striking one (in a man weighing about 140 lbs.) has recently been attained, of 7.1 litres in 13.1 secs.

is determined by the amount of alkali within it capable of neutralising the acid products of its activity. We have heard, of recent years, a great deal about the buffers which maintain a constancy in the hydrogen ion concentration of the blood. The buffers of muscle, fulfilling the same function, must be just as effective as, and their total amount far greater than, those of the blood. Training may consist, to some degree, in an increase in the amount and disposition of the available alkali.

CO_2 ELIMINATION AND RETENTION

This sudden production of acid, as pointed out above, is the explanation of the large amounts of CO_2 that come off during the exercise and immediately after it (fig. 1). When the lactic acid is removed in recovery, the same quantity of CO_2 must be retained as was originally eliminated (fig. 2); sodium lactate must become sodium bicarbonate again. Consequently, we find very low respiratory quotients in the later stages of recovery. The CO_2 retained is a measure of the lactic acid got rid of. The oxygen used in recovery is a measure of the carbohydrate (or lactic acid) oxidised. The comparison of the two enables us to determine in man the "efficiency" of recovery. Again, we find that only a small fraction of the lactic acid has been oxidised, the value determined for the "efficiency" of recovery being almost identical with that found in the case of isolated frog's muscle; a sufficient reward for the faith that Nature is consistent!

LACTIC ACID IN BLOOD

During and after exercise lactic acid occurs in the blood; during the steady state of continued exercise this lactic acid accumulates to a constant concentration characteristic of the violence of the exercise. In an earlier lecture I gave curves which showed that the speed of the recovery process depends upon the magnitude of the breakdown from which recovery is necessary. The rate of recovery, given an

adequate supply of oxygen, is proportional roughly to the *square of the concentration of lactic acid* in the active muscle. The lactic acid is a sensitive "governor" of oxidation. If we regard the resting oxygen consumption of man as being due to recovery from very small amounts of exercise, slight bodily movements, movements of heart and lungs, muscular tone, then for four times the oxygen consumption, such as occurs in a steady state of ordinary walking, we should expect not four times the lactic acid concentration in the blood, but only twice; for 16 times the oxygen consumption —the limit approached during hard exercise—we should expect not 16 times, but 4 times the lactic acid concentration in the blood. Recent experiments by Long, still only preliminary, tend to confirm this expectation. It will be a very fortunate thing for the body if, when we take 16 times as much exercise, the lactic acid concentration in our blood only rises four times; it would have been very awkward had it been the other way round! The fact is an interesting example of the application to man of one of the by-products of experiments first performed on frogs.

The lactic acid, however, is more interesting when we are not dealing with the steady state. After very severe exercise the lactic acid in the muscles cannot fall very rapidly owing to the inadequacy of the oxygen supply. It diffuses out, therefore, into the blood and all round the body. It reaches a maximum in the blood a few minutes after it has attained its maximum in the muscles (fig. 3). Hence the maximum in the blood is lower than in the muscles. At the particular moment, however, when it is at its maximum in the blood, we may be sure that it is the same in the muscles; equally it is certain to be the same in both towards the end of recovery, when both are becoming constant. It is possible, therefore, by a direct analysis of lactic acid in the blood to ascertain the concentration in the muscles and other soft tissues of the body at two moments: (1) about ten minutes after exercise, and (2) towards the

end of recovery. By such direct analyses, and assuming that about 50 per cent of the body weight is in intimate contact with the blood, it is possible to determine directly —if somewhat roughly—the amount of lactic acid which has disappeared in the recovery process. This may be compared, as in the case of the lactic acid calculated from the CO_2 retention, with the oxygen used in that removal, and it is found, as in the frog's isolated muscle, that the acid is not oxidised; only about one-fifth of the oxygen is used which would be required were all the lactic acid broken down to CO_2 and water. The same ratio for the "efficiency of recovery" is attained in man as in the isolated muscle.

CARBOHYDRATE THE FUEL OF MUSCLE

It has long been discussed whether the proper fuel of muscle is carbohydrate or whether *any* foodstuff may be employed to provide the energy for muscular movement. The most conclusive evidence available, up till recently, was that of the experiments of Krogh and Lindhard, who showed in a beautiful and consistent series of observations that the "mechanical efficiency" is appreciably higher with a high respiratory quotient and on a carbohydrate diet, than it is with a low respiratory quotient when the fuel is mainly fat. They suggested that carbohydrate is the substance actually used by muscle for its activity, and that when fat has to be oxidised to provide the necessary energy, it must first be transformed into carbohydrate, and in that process an appreciable fraction (about 10 per cent) of the energy of the fat is wasted. Meyerhof also has found, in the isolated muscle, a respiratory quotient of about unity during the recovery phase. It was possible, however, that the recovery process might indeed involve the oxidation of carbohydrate only in the isolated muscle, and yet, in the intact animal with its circulation and the interaction of its various organs still at work, fat might equally well be oxidised directly to provide the muscle with

energy. The ordinary method of examining the respiratory quotient in a man carrying out prolonged exercise is not adequate to decide this problem, since a respiratory quotient of (e.g.) 0.85 might be given by the oxidation primarily of carbohydrate, followed later by the restoration of some of the carbohydrate at the expense of fat. It has proved possible, however, by an extension of the methods employed in measuring the oxygen requirement of a short bout of exercise, to isolate the muscular processes from the metabolic changes of the body as a whole. These experiments, made mainly by my colleague Furusawa, have shown quite clearly that the primary fuel of muscle is carbohydrate.

A short bout of exercise is taken, mild to moderately severe, and the total oxygen used and the total CO_2 given out, *during the exercise and in complete recovery from it*, are measured. From these are subtracted the oxygen which would have been used, and the CO_2 which would have been given out, in the same time, reckoned at the resting rate before, or as the average of before and after, the experiment. The differences represent the oxygen and the CO_2 consumed, and produced, as the result of the exercise. Provided the bout of exercise be not too prolonged *the oxygen and the CO_2 are exactly equal:* carbohydrate has been oxidized, and the body has returned, without *any* extra consumption of fat to its original condition. If the exercise be continued for a long time the respiratory quotient of the exercise plus recovery is low: if it be of an intermediate duration the respiratory quotient also is intermediate: if it be very short the respiratory quotient is unity. An *element* of muscular exercise, therefore, is conducted simply at the expense of carbohydrate: while if the exercise be prolonged other metabolic processes are stimulated which presumably restore some of the carbohydrate at the expense of fat. Primarily, however, the fuel of the recovery process in the intact animal, as in the isolated muscle, is carbohydrate.

FACTORS AFFECTING SPEED OF RECOVERY

Among other things the speed of the recovery process depends on the rate at which oxygen can be supplied to the active muscles. This is limited by two factors: first, the total oxygen that can be taken through the lungs into

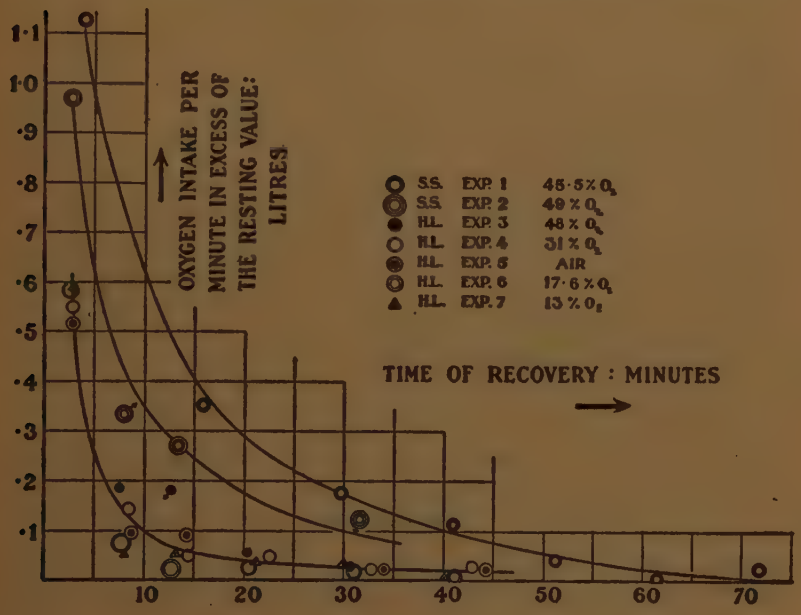

FIG. 12. TO SHOW THE SPEED OF THE RECOVERY PROCESS IN MEN BREATHING GAS MIXTURES RICH (EXPERIMENTS 1 TO 4) AND POOR (EXPERIMENTS 6 AND 7) IN OXYGEN

Note that these curves (especially experiments 3 to 7 on a single subject) do not show a more rapid recovery at higher oxygen pressures. Cf. figure 7. (Hill, Long and Lupton, 1924.)

the blood and circulated by the heart; second, the local circulation to the part involved. This factor of oxygen supply is not usually important in a healthy man *after* exercise is over: once the initial rapid drop in the oxygen

intake has occurred the oxygen supply is apparently quite adequate to the needs of the muscles, the circulation rate falls off, the arterial blood is fairly completely saturated, and no increase in the speed of the recovery process occurs if the subject breathes a gas mixture considerably enriched with oxygen (fig. 12). In abnormal conditions of course, as in the isolated muscle, the factor of oxygen supply may be of great importance in determining the speed of the recovery process. In the broader sense, however, all oxidation in muscle is recovery oxidation, and during continued exercise the oxygen intake determines the speed of recovery from previous elements of the exercise. Many observations have been made of the oxygen intake of a man undergoing various forms of severe muscular exercise. The highest value recorded while breathing air is 4.2 litres per minute; breathing 50 per cent oxygen, very nearly 6 litres has been reached, and that by a subject who has never reached more than about 3.8 litres in air. The only possible reason why more oxygen can be taken in, when breathing oxygen, is that the blood is not completely saturated during very severe exercise when breathing air; the greater saturation, however, of the coronary blood, when breathing oxygen, may then result in greater cardiac activity. The magnitude of the oxygen intake is determined mainly by the capacity of the heart, and I will give later a calculation showing what this number means in heart output. The other factor determining the speed of the recovery process is the local supply of blood to the muscles actually involved. Lindhard showed that in such exercise as holding the body with arms bent, on rings in a gymnasium, the blood supply to the active muscles of the arm is almost completely cut off. The whole of the oxygen required had to be used after the exertion was over. In running the supply of blood to the active muscles is particularly easy, as they are never rigid and their movements are rapid.

HEART OUTPUT FROM OXYGEN INTAKE

The values of the oxygen intake during severe exercise allow a striking—if approximate—calculation of the output of the heart. Assuming, as was the case in the subject who consumed 5.9 litres of oxygen per minute, an oxygen capacity of 21 cc. per 100 cc. of blood, and an average utilisation coefficient of 75 per cent (a value as high as has even been recorded), then the actual oxygen taken in must have required 37.5 litres of blood per minute to carry it. This amount of blood has been ejected from the heart twice, from the right side once and from the left side once; altogether, therefore, 75 litres of blood—about 17 gallons, about 120 times the heart's own volume—have been pumped out in every minute. Even assuming a utilisation coefficient of 100 per cent, 56 litres (12½ gallons) of blood must have been pumped together from the two sides of the heart. Compare these volumes with the amount of water which a bath tap can pour out in a minute, even when turned full on. In such exercise the heart-rate —recorded with a string galvanometer—is about 180, which means that each side of the heart ejects some 200 cc. per beat. There is no possible flaw in the argument or calculation, otherwise it would be difficult to believe the conclusion. It is little wonder that the heart sometimes cannot stand the strain.

ENERGY REQUIREMENT OF HEART

It is possible, by an approximate calculation to determine the oxygen consumption of the heart during such exercise. The calculated output of blood, multiplied by the blood pressure, gives us the work done; assuming a mechanical efficiency of 20 per cent, which is a high value under such conditions, the total energy used by the heart can be calculated. The provision of this energy requires the consumption of oxygen, and it would appear that the

oxygen requirement of the heart during such exercise as that described above is about 300 cc. per minute—about half its own volume. Assuming a utilisation coefficient of 75 per cent and an oxygen capacity as before, this requires two litres of blood to pass through the coronary vessels of the heart per minute. This volume of oxygen, actually used by the heart, is almost equal (per gram) to that *required* (*but not obtained*) by voluntary muscle during very violent exercise. The muscle has to stop within a minute, owing to oxygen-want; the heart, however, owing to its better oxygen supply, when the coronary circulation is efficient, is able to keep up an output of this order for long periods. It would seem possible that a deciding factor in the capacity of a man for severe prolonged exercise may often be the efficiency of his coronary circulation.

OTHER FACTORS IN RECOVERY

The recovery process depends also on other factors. In a previous lecture I showed how in the isolated muscle it depends on the hydrogen ion concentration. Deep breathing, therefore, sweeping away the CO_2 and keeping the body alkaline, may be advantageous to the quickness of the recovery process. It must depend also upon the presence of oxidative catalysts, such as those recently described by Hopkins, Meyerhof, Warburg, and others. It is likely that the oxidising faculty of tissues will vary from individual to individual. It may be, therefore, that important divergences from the normal will be found in persons suffering from various forms of dyspnoea, in respect of their oxidative metabolic power. Possibly athletes, and people accustomed to heavy work, will develop this side of their metabolic activities. Recent work in Hopkins' laboratory has shown that haemoglobin has a very distinct catalysing power in the oxidation of unsaturated fats. The dyspnoea so often associated with anaemia may in

some cases, be due to the absence not only of an adequate oxygen supply and of adequate blood and tissue buffers, but of an adequate amount of some oxidising catalyst. Recent work by Warburg and his colleagues has shown that many forms of biological oxidation probably occur as surface phenomena, catalysed by iron atoms embedded in the surface; the absence of the iron, or its removal from activity by physical or chemical means, will hinder or prevent oxidation, as also will displacement of the oxidisable bodies, by narcotics or other substances, from the active surfaces where oxidation goes on. Imperfect metabolism of iron, excretion of it, its combination with abnormal metabolites, the displacement of the bodies to be oxidised away from the oxidising surfaces might all lead, therefore, to an imperfect and slow recovery from exertion, to dyspnoea associated with exercise.

APPLICATIONS

All of us can suffer from dyspnoea and all of us can exhaust ourselves very rapidly; the finest athlete in the world may be almost incapable of movement within 50 seconds from the beginning of a race. The same degree, however, of exhaustion may be produced by a much lower level of exercise, no more rapidly but just as effectively, in a person of lower oxidative faculty or with poorer buffers in his tissue. When I was lecturing recently in Holland on this subject it was remarked, after one of my lectures, that it was typical of an Englishman, when he had found an interesting bit of physiology, immediately to want to apply it to sport. Perhaps some of you will sympathise with the motive, even if the charge be true. There is a better one, however; athletes and healthy men give us the cleanest experiments. If one took a patient from the hospital and made him work till he could barely move, one could never be sure (*a*) that he had really driven himself to his limit—it requires an athlete to know how to

exhaust himself; (*b*) that one would not kill him; and (*c*) what the cause of his stopping was. With young athletic people one may be sure that they really have gone "all out," moderately certain of not killing them, and practically certain that their stoppage is due to oxygen-want and to lactic acid in their muscles. Quantitatively the phenomena of exhaustion may be widely different, qualitatively they are the same, in your athlete, in your normal man, in your dyspnoeic patient. You can only *observe* your patient, but you can *experiment* with your athlete; you can "try out" on him the facts and theories which you have reached with frogs. There I must leave it, and be grateful if the young athletes in their turn can suggest further experiments on frogs.

The work which I have described to you today is largely due to the devotion and enterprise of my friend and colleague Hartley Lupton. Lupton, alas, at the early age of 32, died on September 6th, 1924, of a cruel disease, after distress and suffering bravely and cheerfully borne. He did not live to see the published account of his investigations, but I hope that they will remain associated with his name. He wrote me a fortnight before his death saying how he would have loved to be in this place, to hear me discuss this work with you. Never did he admit that he would not be back to his beloved apparatus in a few weeks' time. His work will survive him, and will result, I am happy to believe, some day in the alleviation of human suffering, insofar as it leads to a better understanding of the processes of the living healthy body: it has its implication in medicine, as well as in physiology: it will prove a sufficient monument to Lupton's devotion.

You have done me a great honour in inviting me to come across the sea, which separates but does not divide our countries, to speak to you. I am very sensible of that honour. I have many reasons indeed to be grateful to you and to your countrymen. I have the happiest

memories of friendship and coöperation with Americans, in the laboratories at Cambridge, Manchester and London, and in other places and circumstances during the war. University College also, from which I come, owes much, very much, to the generosity of the Rockefeller Foundation. And to all this you have added the singular kindness with which you have received me, and the patience and forbearance with which you have heard me. Perhaps some of you may, some day, add to that kindness by coming to work with me in England.

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